

The Use of Vasopressin in In-Hospital Cardiac Arrest

Edward Chen

A. Statement of study purpose and rationale

The purpose of this study is to evaluate the potential USE of vasopressin as an adjunct to epinephrine in the resuscitation of patients who experience cardiac arrest. Approximately half a million people each year suffer from sudden cardiac death in this country [1]. The outcome of resuscitation efforts has been improved over the last two decades by an increase in bystander cardiopulmonary resuscitation (CPR), improved emergency medical service (EMS) response times, and prompt initiation of the American Heart Association's (AHA) Advanced Cardiac Life Support (ACLS) protocols. Survival rates, however, remain low: between 3-5% for out-of-hospital cardiac arrests and 10-15% for in-hospital cardiac arrests [1].

In the ACLS protocols for cardiac arrest, epinephrine is used as the vasopressor agent of choice to restore circulation adequate for organ perfusion. The use of this drug is rooted in animal data and empirical observations in humans. Although the administration of epinephrine in cardiac arrest resuscitation has become the standard of care, the only prospective trial comparing epinephrine to a placebo showed no difference in immediate survival or survival to discharge [11]. This has led the AHA to conclude that epinephrine represents "...a last desperate effort to resuscitate patients with a very poor chance of survival [2]."

Vasopressin (also known as antidiuretic hormone, or ADH) is an endogenously produced hormone that regulates serum osmolarity and blood volume by increasing water reabsorption in the kidneys. It also acts as a vasoconstrictor in vitro causing isolated smooth muscle cells to contract and in vivo in animal and human studies causing an elevation in arterial blood pressure [4]. Vasopressin is used clinically to treat patients with central diabetes insipidus, and to reduce bleeding in patients with bleeding esophageal varices from portal hypertension [10].

Endogenous levels of vasopressin are increased in many states of extreme stress, including severe pain, vasovagal syncope, surgery, myocardial infarction, and septic and hemorrhagic shock. One study has demonstrated that levels of vasopressin are increased in patients undergoing CPR and are significantly higher in patients who were successfully resuscitated than in non-resuscitated patients [9]. Conversely, levels of endogenous catecholamines are negatively associated with survival [6]. Studies in animals have demonstrated that vasopressin is superior to epinephrine in improving vital organ blood flow, as well as hastening return of spontaneous circulation (ROSC) during CPR [5, 8]. Vasopressin may be an ideal vasopressor in cardiac arrest because it selectively shunts blood flow from non-vital organs such as fat, skin, skeletal muscle, and intestine, and increases flow to heart, liver, kidney, and especially brain [8].

Preliminary data in the form of case reports demonstrate that vasopressin is superior to epinephrine in resuscitating patients in refractory cardiac arrests [7]. Vasopressin was administered to 8 patients who did not respond to epinephrine or other standard resuscitation measures. All patients had restored spontaneous circulation and 3 survived to discharge with intact neurological function [7].

The combination of epinephrine and vasopressin has been evaluated in maintaining circulatory stability in brain-dead patients [3]. The two agents have synergistic effects on increasing mean arterial pressure, cardiac index, and total peripheral resistance. Additionally, survival is increased from an average of 2 days when either drug is used alone to 24 days when both are used.

The present study will further explore the role of vasopressin as a -vasopressor agent in in-hospital cardiac arrest. Vasopressin will be evaluated as an adjunct to epinephrine in the ACLS protocols used in refractory arrests at CPMC in a prospective trial. This assessment will be achieved by comparing the efficacy of vasopressin to that of placebo when given to patients who are unresponsive to epinephrine.

B. Description of study design and statistical analysis

a. Patient selection

This is a randomized, double-blinded, placebo controlled study that will seek to enroll approximately 100 patients who have experienced cardiac arrest (defined as the sudden loss of spontaneous circulation). Vasopressin will be analyzed in the following types of arrests: ventricular fibrillation, unstable ventricular tachycardia, pulseless electrical activity, bradycardia, and asystole. Included in the study will be adult in-hospital patients who are in cardiac arrest, who have received an attempt at resuscitation using one or more of the ACLS protocols, and who demonstrate an inadequate response to epinephrine. Patients will be excluded if they are minors, are pregnant, have advanced directives to do not resuscitate (DNR), or have irreversible cardiac arrest (rigor mortis, core temperature < 90 OF, or elapsed time from start of cardiac arrest to activation of ACLS protocol > 20 minutes).

Since the patients will be those who are unresponsive during arrest, and successful resuscitation requires rapid action, advanced consent will not be possible. The ethical rationale of using vasopressin in this study without prior consent is based on the premise that the patients have failed to respond to conventional therapy, and any effective alternatives are as of yet unrecognized. The administration of vasopressin at this point offers potential benefit with little if any additional harm.

b. Methods of randomization

At CPMC, when a patient has a witnessed arrest or is discovered pulseless and unresponsive and without a pulse, the emergency system is activated and the arrest team is summoned to the patient's location. The arrest team, lead by a PGY-2 medicine resident (arrest resident), determines the type of arrest that the patient has experienced and attempts resuscitation using the appropriate ACLS protocol (e.g., ventricular fibrillation, unstable ventricular tachycardia, pulseless electrical activity, bradycardia, and asystole). In the protocols, 1 mg. of epinephrine is given every 3-5 minutes by intravenous push (IVP) to maintain vascular tone. In the study, if resuscitation is not successful within 5 minutes after the initial dose of epinephrine is given, the patients will be randomized to receive either placebo (normal saline) or vasopressin (40 units) by IVP. The ACLS guidelines will otherwise be followed until successful ROSC, or the decision is made by the arrest team to terminate resuscitative efforts. Syringes containing either vasopressin (40 units) in 10 cc of normal saline or normal saline alone (placebo) will be made in advance by Dr. Hardin and will be placed by random assignment in the portable arrest defibrillator used by the arrest resident.

c. Number of repeated measurements

During all cardiac arrests at CPMC patients are routinely monitored for vital signs (i.e., pulse, blood pressure, spontaneous respiration rate, and temperature). In addition, electrocardiac telemetry and blood analyses are performed. The study will not require patients to undergo additional RAI testing except for a subset of patients who will have end bus serum vasopressin levels measured from blood samples that are routinely drawn (see "Description of study procedures" below).

d. Statistical analysis

The primary endpoint in this study will be survival at one hour. Additional outcomes to be assessed will include time from start of resuscitative measures to ROSC, and survival to discharge from the hospital. We estimate recruiting approximately 50-60 patients per year. Power analysis indicates that 50 arrests randomized equally to receive either vasopressin or placebo, will have 80% power in a two-tailed test of the difference of proportions surviving, at a type I error rate of 5%, to detect a treatment related improvement of 50% survival, given a rate of survival of 15% in the control group. While this represents a "large" effect size, preliminary data and limitations of available resources indicate that these outcome rates are within reason and feasible to achieve. Dr. Donald McMahon of the Irving Center for Clinical Research assisted with these calculations.

C. Description of study procedures

All patients managed by the arrest team routinely have either a peripheral or central venous catheter placed prior to or during arrest. All intravenous medications (including vasopressin and placebo) can be administered via the catheter. The study will require no additional procedures to be performed on the patients involved.

In a subset of patients, vasopressin levels will be measured to correlate the efficacy of administered vasopressin with endogenous levels. In arrested patients who have blood routinely drawn prior to administering intravenous medications (such as epinephrine), an additional 5 to 10 cc of blood will be taken to assay endogenous vasopressin levels. In those patients who are successfully resuscitated and have further routine phlebotomy, another post-resuscitation vasopressin level will be determined. These determinations will impose no further risk or pain on the patients.

D. Study drug

Vasopressin is an endogenous hormone that has a half-life of 10 to 20 minutes when given intravenously. This peptide is used to treat central diabetes insipidus and bleeding esophageal varices at doses of 510 units per hour. Based on published empirical data of vasopressin in cardiac arrest, we plan to administer vasopressin at a dose of 40 units IW

The side effects of vasopressin are similar to epinephrine and other vasopressors. These include cardiac arrest, arrhythmias, shock, decreased cardiac output, angina, myocardial ischemia, peripheral vasoconstriction, gangrene, circumoral pallor, abdominal cramping, nausea, vomiting, flatus, tremor, vertigo, "pounding" in head, bronchial constriction, sweating, urticaria, and cutaneous gangrene [10].

E. Medical Devices

Not applicable.

F. Study questionnaires

See copy of attached arrest resident questionnaire.

G. Description of study subjects and method of recruitment

All patients who meet the criteria provided in Section B under "Patient selection" will be included in the study. As described in Section B, it will not be possible to obtain prior consent and patients will be enrolled in the study based on failure of conventional therapy and the potential favorable benefit to risk ratio of vasopressin in refractory cardiac arrest. After each arrest, notification of participation in the study will be provided to the surviving patients, family members, and primary physicians. This will be accomplished verbally and in writing (see attached "Notification of Participation in Study" form).

Patients will be recruited without regard to gender, racial, or ethnic identity.

H. Confidentiality of study data

All information obtained during this study and identified with the patient will be kept confidential. The Food and Drug Administration and the manufacturer of vasopressin (Parke-Davis) may have access to patient data but individual identifying information such as patient name and medical record number will remain confidential.

I. Location of study

The study will be conducted on the in-patient wards at CPMC under the close supervision of the investigating physicians, hospital physicians and hospital staff.

J. Risks and and benefits

Given the often fatal outcome of cardiac arrest (especially when a patient is refractory to epinephrine), this study has the potential to characterize a promising adjunct to conventional resuscitative measures. Studies in animals show that vasopressin is superior to epinephrine in CPR at in increasing perfusion of the heart and brain, the two most important factors in recovering spontaneous circulation and neurological function and improving survival [8].

Side effects have been observed in low frequency during prior usage of the drug and are listed in Section D "Study drug". Empirical use of vasopressin in the Cardiothoracic Care Unit, and results of an ongoing trial of vasopressin in septic shock in the Medical Intensive Care Unit and Cardiac Care Unit at CPMC, have not demonstrated any untoward effects -attributable to the use of vasopressin.

K. Alternative therapies

As discussed above the standard treatment for cardiac arrest is the set of ACLS protocols established by the ARA. These protocols will still be routinely followed until or unless a patient is found to be unresponsive to epinephrine.

L. Compensation and costs to subjects

The patient or patient's family will receive no compensation and will not incur additional costs beyond the standard costs for medical care at CPMC.

M. Minors

This study will not include minors.

N. Radiation or radioactive substances

Not applicable.

O. References

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Lay Summary

Title: The Use of Vasopressin in In-Hospital Cardiac Arrest Principal investigator. Donald Landry M.D., Ph.D. Department: Medicine- Renal division

Study - purpose

The purpose of this study is to assess the ability of vasopressin- to improve survival in cardiac arrest. Cardiac arrest results when the heart is unable to support a blood pressure sufficient to sustain life. Approximately half a million Americans have a cardiac arrest annually and despite advances in resuscitation, only 5% to 15% of these people survive. Successful resuscitation depends on bystander cardiopulmonary resuscitation (CPR), rapid response times, and the administration of medications and special procedures. One of the important medications given to revive patients in cardiac arrest is epinephrine, which acts by increasing the blood pressure.

Vasopressin is a hormone produced by the brain. It is often used medically to treat a type of kidney problem (diabetes insipidus), as well as bleeding from the gastrointestinal tract. Research has suggested that giving vasopressin to animals and patients in cardiac arrest may increase blood pressure and improve survival. We have, therefore, designed this study to verify that vasopressin can revive people in cardiac arrest.

Study design

When an in-patient at CPMC is found in cardiac arrest, the emergency system is activated and resuscitation is attempted (unless the patient has an advanced medical directive of "do not resuscitate", DNR). Resuscitation is performed by hospital doctors and nurses using standard American Heart Association guidelines which call for intravenous epinephrine- to be given. Patients who fail to respond to epinephrine are considered to be in refractory cardiac arrest and seldom recover. These epinephrine non-responsive patients will be recruited into the study by randomization to receive either vasopressin or a placebo (sterile salt water). Standard resuscitation protocol will be otherwise followed. Fifty percent of the patients will be assigned to each arm at randomization. Outcomes to be analyzed include a return of normal circulation and patient survival to one hour and to discharge.

Study subjects

Approximately 50-60 patients will be required to demonstrate the presence or absence of an effect. We estimate that this number of patients will accumulate within 1 year. Only adult, non-pregnant patients will be included in the study.

Recruitment method

As described above, patients will be recruited into the study when they are unresponsive to conventional resuscitation measures (i.e., after no response to epinephrine). Since patients are unconscious during cardiac arrest and successful resuscitation requires rapid action, it will not be possible to obtain prior consent from patients, their families, or their primary physician. Enrollment in the study is based on failure of conventional therapy, and the potential favorable survival benefit of vasopressin in refractory cardiac arrest. After each arrest, verbal and written notification of participation in the study will be provided to the surviving patients, family members, and primary physicians.

Study procedures

Patients in cardiac arrest are routinely monitored for blood pressure, heart rate, electrocardiogram, and blood tests (arterial blood gas, complete blood count, and chemistries). Medications during cardiac arrest are administered via an intravenous catheter. Participation in

this study will not result in any additional procedures. Other than receiving a single dose of vasopressin or placebo all patients in the study will receive the standard treatment for cardiac arrest.

Issues

Side effects of vasopressin are similar to those of epinephrine. This agent has been evaluated in animals and humans for two decades and has been used in the intensive care units at CPMC without serious side effects.

**Columbia-Presbyterian Medical Center
Notification of Participation in Study**

The purpose of this letter is to provide you with information about the study in which you or your family member participated.

Study Title: The Use of Vasopressin in In-Hospital Cardiac Arrest
IRB study number:

Cardiac arrest is a condition in which the heart is no longer able to provide enough blood to maintain life. There are many causes of cardiac arrest and despite decades of research in this area, there are few effective treatments for resuscitating people who experience cardiac arrest. Consequently, less than 10% of all people who suffer a cardiac arrest survive.

You or your family member were/was chosen to participate in this study because you/he/she have/has suffered a cardiac arrest while in the hospital and did not respond to conventional therapy. When you or your family member did not recover despite attempts by the hospital doctors to resuscitate you/him/her, the hormone vasopressin or a placebo (sterile salt water) was given. Vasopressin is a hormone made by the body to maintain blood volume and blood pressure. In most people who have cardiac arrest, the body produces more vasopressin, which causes the kidneys to increase blood pressure and volume. However, research has shown that the patients who cannot be revived from cardiac arrest make less vasopressin than those who can be revived. This has led other investigators to give vasopressin to a limited number of people who have had a cardiac arrest. Their initial results showed that by giving vasopressin they were able to revive several people who would have otherwise died.

The study in which you or your family member has participated is intended to confirm the preliminary work that shows that vasopressin can save lives when used in cardiac arrest. Similar to the other drugs given during cardiac arrest, vasopressin is given by intravenous injection. Other than receiving vasopressin or placebo, no measures were taken that differ from standard protocol in cardiac arrest. No extra tests were performed or additional drugs were given to you/him/her.

The risks of this study are limited to the side effects of vasopressin. These potential side effects, which are all rare, include water overload, tremors, allergic reactions, and abdominal cramps. There is a theoretical risk of decreasing blood supply to the heart which may lead to a worse cardiac rhythm or heart attack. Again, although these risks are possible, you or your family member was unresponsive to other attempts at resuscitation and would have died. We believe that vasopressin offers hope in this desperate situation.

Participation in this study may or may not have helped you or your family member survive the cardiac arrest. Doctors are unable to rescue the majority of patients who have a cardiac arrest regardless of which medications are given. However, this study may help doctors to treat cardiac arrest in the future. There will be no additional costs to you or your family member. Also, there will be no monetary compensation for participation in this study.

Any information obtained during this study including the identity of you or your family member will be kept confidential. The Food and Drug Administration and the manufacturer of vasopressin may have access to the medical records related to this study. If so, the name and hospital record number of you or your family member will remain confidential.

If you have any questions, please call one of the following investigators:

Dr. Jeff Hardin (212) 305-2323
Dr. Edward Chen (212) 305-2323
Dr. Jeffrey Gold (212) 305-2323
Dr. Boyd Hehn (212) 305-2323

Questionnaire for Vasopressin in Cardiac Arrest Study

Patient Name: _____ Study Drug _____
 MRN: _____
 Arrest Resident: _____
 Date: _____
 Time: _____
 Hospital location: _____

Initial rhythm on electrocardiac monitor: _____

Number of defibrillations: _____

Sequence and amount of intravenous medications (including study drug/placebo):

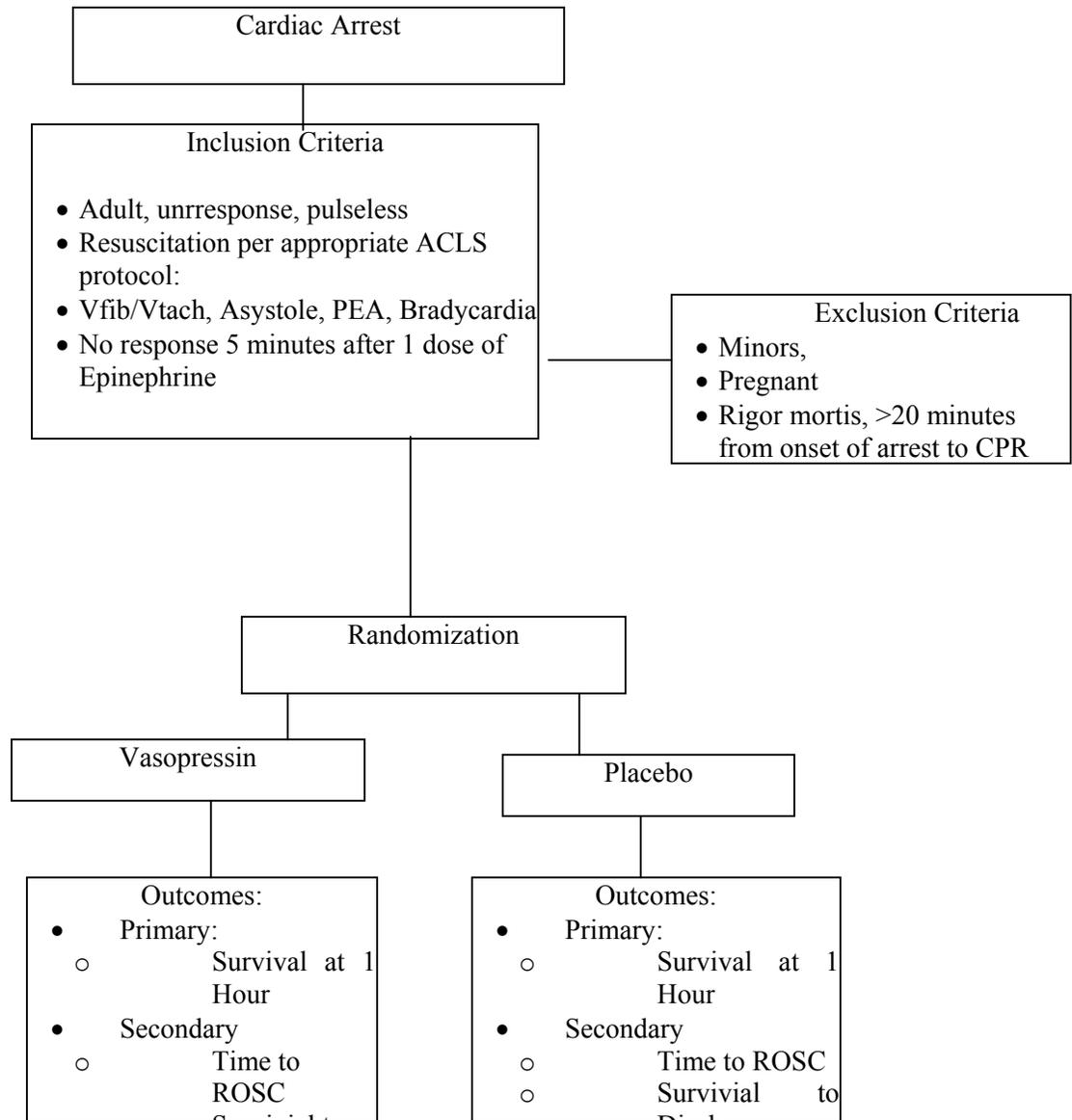
- | | |
|----------|-----------|
| 1. _____ | 8. _____ |
| 2. _____ | 9. _____ |
| 3. _____ | 10. _____ |
| 4. _____ | 11. _____ |
| 5. _____ | 12. _____ |
| 6. _____ | _____ 13. |
| 7. _____ | 14. _____ |

Outcome (e.g., pronounced dead after 30 minutes of resuscitative efforts, or survived"with BP 100/50, HR 105 on Dopamine drip, etc.):

Additional comments:

For further questions please contact Dr. Jeff Hardin, beeper # 1114, or Dr. Edward Chen, Dr. Jeffrey Gold, or Dr. Boyd Hehn.

Trial Profile: The Use of Vasopressin in In-Hospital Cardiac Arrest.



Patient meets criteria for septic shock

Vasopressor started

6 Hour Limit

Patient/Family approached by Primary physician for possibility of Participation

Protocol presentation/ informed consent

Randomization to Vasopressin vs. Placebo

Resolution of Septic Shock

or

Death

Patient Selection

- Septic shock is defined as the presence of a systolic blood pressure of less than 90mm Hg or a decrease of at least 40mm Hg from baseline (prior to the initiation of vasopressor therapy) AND the presence of a hypoperfusion abnormality AND I of more of the SIRS criteria in the setting of a suspected or documented infection.
- SIRS criteria:
 1. Temperature greater than 38 or less than 36 degrees centigrade.
 2. Tachycardia greater than 90 beats per minute.
 3. Tachypnea as defined by a respiratory rate greater than 20 breaths per minute or a PaCO₂ of less than 32mm Hg.
 4. A white blood cell count of greater than 12,000/mm³, less than 4,000/MM³ or greater Criteria:than 10 percent band forms.
- Hypoperfusion abnormalities:
 1. Lactic acidosis.
 2. Oliguria (urine output less than 20cc/hour).
 3. Acute change in mental status.
- Enrollment, randomization, and initiation of therapy must occur within 6 hours of the initiation of vasopressor therapy.

Patient Exclusionary Criteria:

- Prior enrollment in this protocol.
- Age less than 20 years.
- Pregnancy.
- Prior documented episode of septic shock.
- Presumed cardiogenic or hypovolemic shock.

Proposal and Protocol

Principal Investigator: Donald Landry, M.D., Ph.D.
Department of Nephrology (212) 305-1890

Other Investigators: Edward Chen, M.D., Department of Medicine
Boyd T. Hehn, M.D., Department of Medicine
Jeffrey A. Gold, M.D., Department of Medicine
Jeff D. Hardin, M.D., Ph.D., Department of Medicine

Statistician: Donald J. McMahon (212) 305-5949

A. Statement of Study Purpose and Rationale

It is estimated that there are approximately 500,000 cases per year in the United States associated with a crude mortality rate of 35 percent, and of these 40 percent will develop shock and increase their mortality rate to 46 percent despite the initiation of prompt and proper supportive and therapeutic measures) Unpublished data from earlier studies demonstrate a decrease in vasopressor dose requirements when low dose vasopressin was administered as an adjunct to standard therapy. Therefore we propose a prospective, randomized, double-blind, placebo controlled study of the use of vasopressin within 6 hours of the initiation of vasopressor therapy in septic shock to examine the effect on mortality.

Current standard therapy for septic shock includes antimicrobial therapy, fluid administration, and in severe cases vasopressor (catecholamine or catechol-like) agents. These vasopressor (vasoconstricting) agent may have deleterious effects including lactic acidosis, gangrene, intestinal ischemia, and acute renal failure, through excessive peripheral arteriolar vasoconstriction, or increasing the underlying metabolic rate and offsetting the increased cardiac output.' Further, a marked resistance to the vasoconstricting effect of catecholamines is frequently observed.

Vasopressin is a nonapeptide released from the posterior pituitary due to either increased plasma osmolality or by hypovolemia and/or hypotension? It is both a potent vasoconstrictor acting through V₁ receptors, and acts of the renal collecting ducts through V₂ receptors to increase the permeability of cell membrane to water. Both of these mechanisms allow for correction of any of the three above events. A large body of data from experimental animal models supports the conclusion that vasopressin helps maintain arterial blood pressure during episodes of severe hypovolemia/hypotension.' Vasopressin is synthesized in the perikarya of magnocellular neurons in the SON and PVN, and the process of axonal transport of vasopressin-containing granules from the site of production to the posterior pituitary requires 30 minutes.³ With continuous stimulation of the posterior pituitary by vasopressin-releasing stimuli, diminished hormone release occurs. Preliminary data from ad unct studies (not published) have established that circulating levels of vasopressin (ADH) are abnormally low in human patients with septic shock. There is also data to support the synergistic effects of vasopressin and catecholamine vasopressors.' Anecdotal observations of vasopressin given to individuals on vasopressors demonstrated a decrease in the levels of vasopressors given. Examination of data from an earlier study in which the use of low-dose vasopressin to decrease vasopressor requirements was examined, but late in the course of septic shock, demonstrated both efficacy of the intervention as well as its safety. The data also anecdotally demonstrates improvement in some of the indices of hypoperfusion. However, the protocol was limited by the requirement of a Swan-Ganz catheter for entry into the study, the use of vasopressin late in the course of septic shock when the subjects had marked vasopressor requirements, as well as being limited to a 2 hour period of observation before unmasking took place and crossover from placebo to vasopressin was allowed.

We now propose to examine the use of low-dose vasopressin early in the course of septic shock, within 6 hours of vasopressor support being initiated. Patients will be selected by application of the clinical definitions of septic shock and randomized to receive either low-dose vasopressin (0.1U/minute IVSS) or placebo in addition to the other standard therapies. The primary endpoint of this study will be the effect of vasopressin on patient mortality. Study participation by an individual shall be over when either resolution of septic shock or death has occurred. Resolution of septic shock shall be defined as a systolic blood pressure of greater than 90 mm Hg not requiring vasopressor therapy. Resolution of oliguria or lactic acidosis, while secondary endpoints, will not be required. Acute tubular necrosis may prolong the renal recovery phase despite the presence of adequate perfusion as demonstrated by a systolic blood pressure greater than 90 mm Hg.

B. Description of Study Design and Statistical Analysis:

The study shall be a prospective, randomized, double-masked placebo controlled trial that will take place in the Columbia Presbyterian Medical Center Medical Intensive Care Unit (MICU), Critical Care Unit (CCU), Surgical Intensive Care Unit (SICU), and the Allen Pavilion ICU.

Patient vital statistics will be kept with accordance to standard Intensive Care Unit practice, and will be used to monitor the effects of vasopressin on time to resolution of oliguria and lactic acidosis. At the time of entry into the study, a vasopressin level will be drawn prior to the initiation of vasopressin or placebo and will be examined retrospectively at the end of the study. These samples will be run in a single batch after completion of the study and are only to document a vasopressin-depleted state that is believed to occur at the onset of septic shock. The primary end-point of the study is defined as either resolution of septic shock or death, at which time the study drug will be stopped. Resolution of septic shock is defined as a systolic blood pressure of greater than 90 mm. Hg not requiring vasopressor therapy.

At the time of randomization, patients will either receive vasopressin or placebo as a constant rate infusion. Infusion mixtures will be made by the ICU nursing staff from a set of prenumbered, randomized, batched vials of either vasopressin or placebo. These vials will have been pre-made by the research pharmacy and assigned batch numbers according to the predetermined randomization order. Neither the investigators nor the physicians caring for the patient will have knowledge of the contents (either vasopressin or placebo), until completion of the trial when outcomes are being determined for both arms of the trial. All other clinical treatment decisions will be made by the patient's primary physician or the ICU staff.

Secondary endpoints will have data collected as either urine output in 2 hour intervals (standard CPMC ICU practice) or serum arterial lactate levels at 6 hour intervals until lactic acidosis has cleared. Other endpoint will have data collected from either the CPMC Laboratory system or the patients chart.

The proposed study seeks to establish whether medical management of septic shock with vasopressin significantly improves mortality. Current published estimates of septic shock mortality in tertiary care ICU settings range from 10 to 90 percent. A recent large scale study of septic shock mortality¹ provides a point estimate of 46 percent: we will use this estimate as the base rate for our power analysis and sample size calculation. We assume that a reduction in mortality from 46 to 30 percent will represent a clinically meaningful reduction in septic shock mortality, and further that the deaths will be distributed in a 1:2 ratio between the treated and placebo conditions. A two-sided χ^2 test with a type I error rate of 5 percent and 80 percent power will require 48 patients to reject the null hypothesis for the alternative hypothesis meeting our assumptions. This represents a large effect size: a 3.6-fold improvement in outcome associated with the treated condition relative to the placebo condition.

C. Study Procedure

After patients have been deemed eligible for entry (refer to G for enrollment criteria) and informed consent has been obtained from the patient, the patient's surrogate, or the patient's family, the patient will be randomized to receive either vasopressin or placebo by constant rate infusion.

Patient vital statistics, and urinary output will be kept in accordance with standard CPMC ICU practices. Arterial lactate levels at 6 hour intervals will be followed until normalization is obtained. At study entry a serum vasopressin level will be drawn prior to initiation of the infusion. These samples will be run in a single batch after completion of the study and are only to document a vasopressin-depleted state that is believed to occur at the onset of septic shock. These samples will not affect patient participation in the study, nor affect the randomization process. All records to be copied from the patient's chart, laboratory computer system, or other patient data sources shall be done by the investigators; either Drs. Gold, Helm, Hardin,,or Chen.

The ICU Nurse will mix either 1 OOU vasopressin/100cc D5W or placebo/100cc D5W and start the infusion at a constant rate of 6cc/hour (0. 1 U vasopressin/minute) that will be continued until the primary study endpoint has been reached. During the period of the study it will be the responsibility of the patients nurse to record the vital statistics and urine output, as is standard practice and will add no significant amount of extra work for the nursing staff. The ICU staff will be responsible for obtaining the pre-study serum vasopressin sample, as well as the arterial lactate levels at 6 hour intervals until lactic acidosis has resolved.

The patient's primary physician or the ICU staff will make all decisions regarding standard therapy - antimicrobial selection, vasopressor agent selection and dosing schedule, use of ventilatory assistance, and all procedures. There are 2 restrictions placed on the primary physician/ICU staff. There can be no change made to the infusion rate of the vasopressin drip, and discontinuation of the infusion other than when death occurs requires consultation with one of the investigators.

Time of participation in this study, once initiated, will be determined by the rapidity of occurrence of the primary endpoint - either resolution of septic shock or death. This will be determined on a patient-by-patient basis. Resolution of septic shock is defined as a systolic blood pressure of greater than 90 mm Hg not requiring vasopressor therapy.

Regarding instrumentation of the study subjects, a method for venous access will have already been secured for the administration of vasopressor agents (typically a central venous line). For continuous blood pressure monitoring during vasopressor therapy, blood gas determinations and frequent blood draws, an indwelling arterial line is typically placed. These modalities both fall within typical ICU practice and are part of the standard of care of patients with septic shock. A Swan-Ganz catheter, which is useful in the management of septic shock is not required for either enrollment or participation in this study.

D. Study Drug

Vasopressin is an endogenous nonapeptide with a short half-life of 17-35 minutes.' Typically used in the treatment of diabetes insipidus either intra nasally or intramuscularly, it has also been used as a vasoconstricting agent in the treatment of variceal bleeding, although in doses of up to 0.9U/min by infusion. In this study, vasopressin will be infused as a constant rate infusion at a rate of 0. 1 U/minute.

There are no reports of anaphylaxis or hypersensitivity reactions to vasopressin. The side effect profile reported with the high-dose intravenous vasopressin used in variceal bleeding are similar to the side effects of the catecholamine vasopressors. These include arrhythmia, cardiac arrest, decreased urinary output, increased systemic vascular resistance, hypertension, and tremor. Anecdotally, none of these side effects have been observed with low-dose vasopressin in another trial, or by the Cardio-Thoracic Care Unit in their use of vasopressin.

E. Medical Devices

Not applicable to this study, other than those devices normally used in an ICU setting.

F. Study Questionnaire

Not applicable to this study.

G. Study Subjects and Method of Recruitment

Potential study subjects will be identified by the primary physician or ICU staff and the investigators notified after the patient, surrogate, or family has been approached by the primary physician or ICU staff regarding when they would be willing to consider an experimental therapy. Once identified, the subject will be evaluated for eligibility for entry into the study based on the criteria below, and only after determination of eligibility is made will the patient, surrogate, or family be approached by the investigator for the purposes of enrollment and the obtaining of informed consent.

a. Patient selection criteria are as follows

Septic shock is defined as a systolic blood pressure of less than 90mm Hg or a decrease of at least 40mm Hg from baseline blood pressure (prior to the initiation of vasopressor agents) AND the presence of a hypoperfusion abnormality as defined by the presence of lactic acidosis or oliguria (urine output less than 20cc/hour) or an acute change in mental status, AND requires the presence of I or more of the following criteria of a temperature of greater than 38 or less than 36 degrees centigrade, tachycardia greater than 90 beats per minute, tachypnea as defined as a respiratory rate of greater than 20 breaths per minute or a PaCO₂ of less than 32mm Hg, or a white blood cell count of greater than 12 '000/MM³ or less than 4,000/mm³ or greater than 10 percent band forms, AND clinical evidence of infection.

Identification, enrollment, randomization and initiation of study drug therapy must occur within 6 hours of the initiation of vasopressor therapy.

Patient exclusionary criteria are as follows:

- Prior enrollment in this protocol.
- Age less than 20 years.
- Pregnancy.
- Prior documented episode of septic shock during this hospitalization.
- Possibility of coincident hypovolemic or cardiogenic shock.

H. Confidentiality

All data for this study shall be collected in the patients chart and will be strictly confidential. Any data copied from the patient's chart or from the CPMC Laboratory computer system will be designated by the study number of the patient. A copy of the number with the proper patient medical record number, name, and date of birth, shall be kept in a confidential file separate from the data collected and used for analysis of the endpoints of the study.

The manufacturer of vasopressin (Parke-Davis) may also have access to the collected patient data, but only identified by the study number. Patient names, medical record numbers, and any other possible identifiers shall be kept strictly confidential.

I. Location of Study

The study will take place within the Columbia Presbyterian Medical Center, specific sites being the Medical Intensive Care Unit (MICU), Critical Care Unit (CCU), Surgical Intensive Care Unit (SICU), and the Allen Pavilion ICU, and shall be open to patient's meeting the criteria for septic shock.

J. Risks and Benefits to the Subjects

There are few possible risks to the use of intravenous vasopressin in these patients, given their hyperdynamic and hypotensive cardiovascular state. These risks include the possibility of cardiac arrest, arrhythmia, tremor, and decreased urinary output. Patients will also have an additional 144 mL of fluid added to their volume state in a 24 hour period from the infusion of the vasopressin, which should not add significantly to the fluid load the patient receives.

The benefits to the patient include the projected decrease in mortality, and the decreased dose of vasopressor agents required with the secondary benefits including increased peripheral perfusion with the earlier return of oxidative metabolism.

K. Alternative Therapies

Vasopressin will be administered in low dose (0.1 U/minute) as an adjunct in addition to the standard therapeutic modalities selected by the physicians caring for the patient. Vasopressin will not be used as a replacement for any of the modalities used for the treatment of septic shock.

L. Compensation and Costs to the Subjects

There is no compensation in this study, nor shall any extra costs be accrued by the patient.

M. Minors and Research Subjects

Not applicable to this study, no minors will be enrolled.

N. Radiation and Radioactive Substances

No applicable to this study.

O. References

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