The effect of vasopressin use to control intradialytic hypotension on systemic interdialytic hypertension.

A. Study Purpose and Rationale

End stage renal disease (ESRD) afflicts over 350,000 people nationwide, and the prevalence is increasing.[1] These patients are at particular risk for developing hypertension, with rate ranging as high as 80% depending on the study population. [2,3] Although the data is contradictory, this hypertension may contribute to the heart attacks, stroke, and early mortality seen in these patients.[4] The lack of consensus on this issue may be a result of the j-curve effect (excess 4 mortality with hypotension as well as hypertension). It has been shown that the inability to excrete excess fluid and resultant hypervolemia contributes to the hypertension seen in patients with ESRD,[5-7] and that blood pressure can be controlled in 80-99% of patients with correction to dry body weight. [8- 13]

Control of volume is not always straightforward. One of the most frequent complications of hemodialysis is hypotension, occurring in 25-50% of patients. [14,15] This limits the amount of fluid that can be removed in one session. Indeed, when confronted with hypotension during hemodialysis, the physician is often forced to administer fluids back to the patient and support intravascular volume, even in the face of total body fluid overload.

The etiology of intradialysis hypotension is multifactorial.. but a body of evidence supports the role of vasodilation, or at a minimum, inability to appropriate vasoconstrict. [16-18] Much attention has been placed on alterations in neurohormonal compensatory mechanisms to account for hypotension. One such mechanism involves vasopressin.

Literature on vasodilatory shock states show growing evidence for the role of vasopressin in supporting blood pressure. Although vasopressin does not play a large role in the maintenance of normal blood pressure, [19,20] in the face of hypotension and hemodynamic compromise, its role in compensatory vasoconstriction is crucial. States of vasopressin deficiency have been associated with intractable hypotension despite high dose adrenergic vasoconstrictor therapy, and even small doses of exogenous vasopressin reverses this state. [21]

Substantial literature shows that patients with ESRD have low levels of vasopressin during hemodialysis. [22,23] This may be due to alterations in afferent sympathetic pathways, or the sudden drop of serum osmolality during hemodialysis. High serum osmolality is the strongest stimulus for vasopressin release in normal states. This may help to explain studies showing a key protective role of constant osmolality in maintaining blood pressure. [24] One study has also demonstrated efficacy of twice daily intranasal vasopressin in reducing intradialysis hypotension. [25]

Reducing the incidence of intradialysis hypotension may allow additional fluid removal and better control of hypotension. This study will examine the effect of intravenous vasopressin during dialysis on hypertension and the sequellae thereof.

B. Study Design and Statistical Analysis

500 patients will be enrolled in a randomized, double blinded, placebo controlled study. Patients will be studied during their regularly scheduled hemodialysis sessions and will continue their current regime with respect to medications, activity, and fluid consumption. Patients will be randomized to two arms. The experimental group will receive vasopressin by intravenous infusion at a rate of 1.2 mU/(kg)(min) for three minutes, followed by a constant infusion rate of 0.6 mU/(kg)(min) for the duration of the dialysis session. The control group will receive only the diluents at the same volume rate.

The patients will be studied throughout the five year duration of the study. Before and after each dialysis session, patients will be weighed and blood pressure recorded. In addition, interviews with

patients and primary doctors to determine medications taken as well as interval medical history between dialysis sessions will be performed.

Primary endpoints of hypertension (as defined by the JNC-VI as SBP>140 or DBP>90), mortality, stroke and myocardial infarction will be recorded, as well as secondary endpoints of reduction in antihypertensive dosages and blood pressure. Dichotomous variables will be analyzed using chi-square analysis, while continuous variables will be analyzed using the t-test.

C. Study Procedures

The study will be conducted over two years. The study will take place during the patients' usually scheduled dialysis sessions. Prior to enrollment into the study, a medical examination will be performed to rule out presence of exclusion criteria. Vasopressin or placebo will be infused through the venous limb of the dialysis circuit; therefore additional intravenous access will not be required.

At the initiation of dialysis, vasopressin or placebo (identity unknown to staff, investigators and patient) will be infused through the venous limb of the dialysis circuit. During dialysis, blood pressure and heart rate will be recorded every 15 minutes, and the type and volume of fluids infused will be recorded. Hypotensive episodes will be treated as per standard protocol of the hemodialysis unit. In addition, during the first hypotensive episode for a patient, an electrocardiogram will be performed and compared to baseline EKG. Vasopressin will be discontinued for any acute changes.

D. Study Drugs

Vasopressin will be administered by intravenous infusion at a rate of 1.2 mU/(kg)(min) for three minutes, followed by a constant infusion rate of 0.6 mU/(kg)(min) for the duration of the dialysis session. This low dose infusion is consistent with the dose used to treat vasodilatory shock. Several studies of vasopressin use in these states have shown no substantial untoward effects. [9,26] Additional data from this institution have shown that in 18 healthy subjects who received vasopressin at this level, the only reported side effects were skin pallor, sensation of warmth and mild abdominal cramping.

Vasopressin use at levels substantially higher and longer than those used in this study are used to treat esophageal varices and gastrointestinal bleeding. The standard dose for this indication is 6 mU/(kg)(min). Complications at this dose, ten times that used in this study, have occurred rarely and generally after prolonged exposure (greater than 24 hours). These complications include case reports of local gangrene at the site of infusion, upper and lower extremity gangrene, and ischernic colitis. [27-30] Case reports also exist of myocardial infarction after extremely high dose bolus injections (10-20 U). [31-33] Finally, ventricular arrhythmias (ventricular tachycardia, fibrillation, torsade de pointes) have occurred in patients with prolonged QT intervals receiving vasopressin at rates of 6.0-19 mU/(kg)(min). [34-38]

These side effects are not well characterized, however. In one of the few randomized controlled trials of vasopressin therapy, 29 patients received a dose of 10 mU/(kg)(min) and were compared to 31 patients receiving placebo. The only significant difference in complication was increased incidence of abdominal cramping in the vasopressin group (seven versus one in the control group).

E. Medical Devices

No additional medical devices will be employed in this study.

F. Study Questionnaires

No questionnaires will be used in this study.

G. Study Subjects

Patients undergoing hemodialysis with a creatinine clearance of less than 10 ml/minute will be considered for enrollment. The charts of these patients will be screened and those that have had hypotensive events requiring intervention in three or more of six consecutive hemodialysis sessions will be eliaible for enrollment.

- Patients who meet the following criteria will be excluded from the study:
- Age less than 18 or greater than 75.
- Active vascular disease including active angina, claudication, transient ischemic attacks, ischemic colitis, or Raynaud's disease.
- Long QT syndrome.
- SBP>200 or DBP> 110

H. Recruitment of Subjects

Patients with ESRD on chronic hemodialysis three times weekly will be recruited from the chronic hemodialysis units of New York Presbyterian Hospital and Columbia University. A member of the study team will invite eligible patients to participate during one of their regularly scheduled visits.

I. Confidentiality of Study Data

All subjects will be assigned a code number that will be used for recording data. The assignments and data will be stored in a secure location.

J. Potential Conflict of Interest

There are no conflicts of interest.

K. Location of Study

This study will be conducted at the chronic Hemodialysis Units of New York Presbyterian Hospital and Columbia University.

L. Potential Risks

Study subjects may be at extremely low risk for skin pallor, abdominal cramping, myocardial ischemia or ventricular arrhythmias.

M. Potential Benefits

Potential short-term benefits to subjects include decreased incidence of intradialytic hypotension, with fewer symptoms related to hypotension (nausea, cramping, dizziness, etc.). Potential longterm benefits to subjects include better control of hypertension with subsequent decrease in incidence of myocardial infarction and stroke.

N. Alternative Therapies

There are no alternative therapies.

O. Compensation of Subjects

There will be no compensation for participation in this study.

P. Costs to Subjects

There will be no cost to participation in this study.

Q. Minors as Research Sub6ects

Minors are not included in this study.

R. Radiation or Radioactive Substances

No radioactive substances are involved in this study.

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