

Changes In Brain Natriuretic Peptide Concentrations During Dialysis

Aliza Thompson

A. Study Purpose and Rationale

Brain natriuretic peptide (BNP) is secreted largely by the cardiac ventricle with resulting natriuresis and vasodilatation. Elevated levels of BNP have been documented in states of volume excess. It has been investigated as a marker of left ventricular hypertrophy and used as a predictor of cardiovascular morbidity and mortality in congestive heart failure (CHF) and end stage renal disease (ESRD). Attempts have been made to use BNP as a guide for the intensification of therapy for heart failure. Finally, BNP's synthetic analogue, nesiritide, is now being used in the management of CHF.

Despite the widespread clinical interest in BNP, little is known about the peptide's stimuli for secretion and the reasons for its elevation in ESRD and CHF. A transient increase in BNP levels occurs with stretching of the hypertrophied rat ventricle. Some investigators have documented a decline in BNP levels with dialysis and suggest a role for BNP as a sensor of volume status. Other studies have shown no such response to volume changes. Much more needs to be learned. This study will re-examine the relationship between BNP and changes in volume status during dialysis in patients with ESRD.

B. Study Design and Statistical Analysis

The study is divided into 2 parts. In part 1, patients with ESRD will undergo their usual session of dialysis (defined as hemodialysis-ultrafiltration) to achieve their dry weight. In part 2, the same patients will undergo a session of dialysis without net volume removal.

The study was powered at 80% at $p=.05$ using a paired t-test. Data on the changes in BNP levels expected after dialysis were taken from a prior studying showing a mean BNP of 192 ± 24.9 pg/ml prior to dialysis and 167 ± 21.8 pg/ml after dialysis. The mean change in BNP in part 1 will be calculated from the 3 dialysis sessions. The significance of the changes in BNP occurring with dialysis will be assessed by a two-sided paired t-test.

C. Study Procedure

Patients with ESRD will undergo dialysis on their usual dialysis day to achieve their predetermined dry weight. BNP levels will be measured within a 30 minute period prior to dialysis and at the conclusion of dialysis on 3 separate dialysis days. After collection of all data, the change in BNP levels (pre-dialysis minus post-dialysis) will be calculated. If a significant change in BNP levels is observed, the patients will proceed to part 2 of the study. In part 2 of the study, patients will appear on a normally scheduled dialysis day. They will undergo dialysis for 3 hours without net volume removal. BNP levels will be measured within a 30 minute period prior to dialysis and at the end of the 3 hour session. They will subsequently undergo ultrafiltration as needed to achieve their predetermined dry weight.

To determine BNP levels, samples will be drawn into EDTA vacutainers, frozen immediately, centrifuged within 30min and then stored at -80° . BNP levels will be determined using reverse chromatography (seppak C-18 cartridges) and a commercially available RIA kit. BNP levels will also be measured by a HPLC-RIA assay.

D. Study Drugs

Not applicable.

E. Medical Device

Not applicable.

F. Study Questionnaires

Patients will be screened via questionnaire prior to participation in the study to exclude patients ineligible for the study (see exclusion criteria under "study subjects").

G. Study Subjects

11 ESRD patients greater than 18 years of age on dialysis for 6 months or more. Exclusion criteria include: patients with bleeding disorders, patients with recurrent episodes intra-dialytic hypotension, pregnant women.

H. Recruitment of Subjects

Dialysis patients will be recruited by pamphlets handed out at the Columbia-Presbyterian outpatient dialysis center.

I. Confidentiality of Study Data

All study data will be coded. Each study subject will be assigned a unique code. Data will be stored in a secure location, accessible only to the investigators involved in the study.

J. Potential Conflict of Interest

Neither the University nor any involved investigator has a proprietary interest in the peptide under investigation or stands to benefit financially in any other way from the results of the investigation.

K. Location of the Study

The study will be conducted in the Columbia-Presbyterian outpatient dialysis center.

L. Potential Risks

Patients will be exposed to a lengthened dialysis session in part 2 of the study. Isolated ultrafiltration carries a risk of hypotension, though diminished relative to the risk of hypotension with hemodialysis. There is a potential increased risk of infection and bleeding as fistula access and anticoagulation would be needed for a longer period of time. The incidence of muscle cramps, nausea and vomiting that occurs during dialysis should not be increased as the rate of fluid removal and solute removal will not be increased.

M. Potential Benefits

As a participant in this study you may not benefit as a result of your participation in this study. However your participation will allow the medical community to better understand the significance of elevated BNP levels in dialysis patients and to perhaps apply that understanding to improve morbidity and mortality in this population.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

Monetary compensation will be provided to subjects who participate in the proposed part 2 of the study. Subjects will receive \$75 in the form of a check to be received 6-8 weeks after participation in the study. Payments will not be pro-rated.

P. Costs to Subjects.

None.

Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Not applicable.

S. References

Haug C, Metzle A, Steffgen J, Grunert A: Changes in Brain Natriuretic Peptide and Atrial Natriuretic Peptide Plasma Concentrations during Hemodialysis in Patients with Chronic Renal Failure. *Horm. metab. Res* 26: 246-249,1994.

Jensen KT, Carstens J, Ivarsen P, Pedersen EB: A New, Fast and Reliable Radioimmunoassay of Brain Natriuretic Peptide in Human Plasma. Reference Values in Healthy Subjects and in Patients with Different Diseases. *Scandinavian Journal of Clinical Laboratory Investigation* 57: 529-540, 1997.

Kinnunen P, Vuolteenaho O, Rushkoaho H: Mechanism of Atrial and Brain Natriuretic Peptide Release from Rat Ventricle Myocardium: Effect of Stretching. *Endocrinology* 132: 1961- 1970, 1993.

Mallamaci F, Zoccali C, Tripepi G et al: Diagnostic Potential of Cardiac Natriuretic Peptides in Dialysis Patients. *Kidney International* 59: 1159- 1566, 2201.

Troughton R, Frampton C, Yandle T et al: Treatment of Heart Failure Guided by Plasma Aminoterminal Brain Natriuretic Peptide (N-BNP) Concentrations. *Lancet* 355: 1126-1130, 2000.

Yandle TG, Richards AM, Gilbert A et al: Assay of Brain Natriuretic Peptide (BNP) in Human Plasma: Evidence for High Molecular Weight BNP as a Major Plasma Component in Heart Failure. *Journal of Clinical Endocrinology and Metabolism* 76 (4): 832-838, 1993.

Yoshimura M, Yasue H, Morita E et al: Hemodynamic, Renal, and Hormonal Responses to Brain Natriuretic Peptide Infusion in Patients with Congestive Heart Failure. *Circulation* 84 (4): 1581-1588, 1991.

Zoccali C, Mallamaci F, Benedetto F et al: Cardiac Natriuretic Peptides are Related to Left Ventricular Mass and Function and Predict Mortality in Dialysis Patients. *J Am Soc Nephrol* 12: 1508-1515, 2001.