Effect of Hemodialysis on Myocardial Performance and Cardiovascular Outcomes in End-Stage Renal Disease Patients with Left Ventricular Dysfunction: A Retrospective Analysis

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A. Study Purpose and Rationale

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD) [1-4] as well as those with severe chronic renal failure not yet requiring dialysis [5-9]. The USRDS 2003 Annual Data Report showed that mortality rates remain above 20 percent per year with the use of dialysis, with more than half of the deaths related to cardiovascular disease [1]. In 2004, Go et al found that a reduced estimated GFR was associated with increased risks of death, cardiovascular events, and hospitalization. This was independent of known risk factors, a history of cardiovascular disease, and the presence of documented proteinuria. The risk of having a cardiovascular event increased *as* the GFR declined, up to a 343 percent increase with an estimated GFR of less than 15 ml per minute per 1.73 m^2 (ESRD) [5]. Given the staggering numbers of patients requiring dialysis, estimated at greater than 300,000 Americans [1], death from cardiovascular causes presents a major public health problem.

Congestive Heart Failure is extremely common in patients with Chronic Kidney Disease, contributing to overall cardiovascular morbidity and mortality in this population. Approximately 40% of patients with CKD have CHF and CHF is about 15 times more common in those with CKD than in those with normal renal function. These statistics are consistent with the Third National Health and Nutrition Examination Study (NHANES III), representing a cross-sectional sample of the U.S. population aged 18-64 [10,11]. In the elderly population specifically, Collins found that amongst Medicare patients at least 67 years old who advanced to ESRD, 70% had a diagnosis of CHF at the start of dialysis [12]. Often related to the diastolic dysfunction associated with CHF, left ventricular hypertrophy has been shown to be an independent risk factor for cardiovascular mortality in patients with ESRD [13, 14]. In fact, cardiovascular structural and functional abnormalities occur at impressive rates in patients with ESRD, with only 16% of patients having normal echocardiographic findings at dialysis initiation [13].

The impact of heart failure on survival in ESRD patients is striking, as the presence of heart failure is associated with a higher adjusted risk of death compared with having known coronary heart disease in new ESRD patients [15]. Several studies have looked at therapies that aim to reduce the structural cardiovascular abnormalities seen on echocardiograms in patients with ESRD, with the hope of impacting the high rates of cardiovascular morbidity and mortality in this population. In addition to the classical cardiac risk factors of hypertension, dyslipidemia, diabetes, obesity, and smoking, these studies have looked at other key factors that are though to play a role in the cardiac damage of uremia, including anemia, malnutrition, elevated C-reactive protein, reduced fibrinolysis, serum calcium-phosphate product, parathyroid hormone, homocysteine, and the cytokines tumor necrosis factor and interleukin-6. As early as 1989, correction of anemia with recombinant erythropoietin was shown by Low et al. to be associated with improvement of left ventricular hypertrophy in patients with ESRD receiving maintenance dialysis [16]. A recent open-label prospective 2005 study extends these results to a population of CKD Stage 4 patients not yet requiring dialysis, where a significant reduction in left ventricular mass index was found after 6 months of recombinant erythropoietin therapy [17]. As another example, Cice *et al.* randomized 114 dialysis patients with dilated cardiomyopathy to receive either carvedilol or a placebo in addition to standard therapy. At 2 years, the carvedilol group had higher ejection fractions and significantly fewer total deaths, cardiovascular deaths, and hospitalizations compared to the placebo group [18]. This study made the argument for routine use of ardioprotective drugs in patients with CKD in order to reduce the high rates of cardiovascular morbidity and mortality.

It is somewhat intuitive that the therapeutic intervention of dialysis itself may improve the abnormalities seen on echocardiograms in patients with ESRD and left ventricular dysfunction. In fact,

improvement in ejection fraction is often clinically observed in this population of patients when they initiate renal replacement therapy, and this is postulated to be due to better volume control, decreased strain, and better filling. Scarce data exists, either in support or contradiction, of this clinical observation. The purpose of this study is to retrospectively evaluate the effect of hemodialysis on ejection fraction in ESRD patients with left ventricular dysfunction (as defined below) who are initiating renal replacement therapy. The hypothesis is that there will be an improvement in left ventricular ejection fraction after 1 year of hemodialysis. The secondary purpose of this study is to examine cardiovascular outcomes in this population to see whether the postulated improvement of ejection fraction with hemodialysis may contribute to a reduction in the widespread morbidity and mortality associated with ESRD.

B. Study Design and Statistical Analysis

This is a retrospective longitudinal study utilizing a database of ESRD patients who initiated hemodialysis at Columbia University Medical Center starting in 1995 and beyond who have available transthoracic echocardiogram results in the WebCIS computer system within 90 days prior to the start of hemodialysis as well as 1 year later (9 months-15 months from the first anniversary of hemodialysis).

Outcomes and Definitions: The primary outcome of the study is change in ejection fraction over 1 year in ESRD patients with left ventricular dysfunction who are initiating and undergoing hemodialysis for the full year, who have never undergone any form of renal replacement therapy before. For the purposes of this study, left ventricular dysfunction is defined *as a left* ventricular ejection fraction of less than 40% on the *pre-initiation of hemodialysis* echocardiogram. Patients that fit this criteria must have a second available echocardiogram result 1 year following initiation of hemodialysis in order to be included in the study. Any echocardiogram falling within the range of 9 months to 15 months from the first anniversary of hemodialysis is acceptable for the *1 year post-hemodialysis* echocardiogram. If there are multiple echocardiograms within this time range, the one that is closest in time to the first anniversary of hemodialysis will be used. Given the somewhat subjective skill associated with reading echocardiograms, and in an effort to minimize error, only patients whose *pre* and *post* echocardiograms are read by the same cardiologist will be included in the study. Transthoracic echocardiograms, performed with two-dimensional ultrasonography, will be the only type of echocardiogram used in this study. The secondary outcome of the study is a composite endpoint that seeks to measure total adverse outcomes associated with cardiovascular morbidity and mortality following 6 months of hemodialysis. This endpoint includes death from any cause, hospitalization for angina pectoris (ICD-9 413), hospitalization for unstable angina (ICD-9 411.1), hospitalization for acute myocardial infarction (ICD-9 410), hospitalization for congestive heart failure (ICD-9 428.0), and any coronary revascularization procedure including coronary artery bypass grafting or percutaneous angioplasty/stenting.

Design: As above, this is a retrospective longitudinal study utilizing Columbia University Medical Center's hemodialysis database for patients that initiated hemodialysis starting in 1995 and beyond. A series of baseline characteristics will be collected on each patient. Categorical variables include gender (male vs. female), race or ethnic group (white, black, Hispanic, Asian, South Asian, other), diabetes mellitus (presence or absence as defined by the use of oral agents, insulin, HbA 1 c >7%, or random blood sugar >200), history of hypertension (presence or absence as defined by the use of anti-hypertensive agents at home), history of angina (presence or absence according to notes in chart/WebCIS), history of unstable angina (presence or absence according to notes in chart/WebCIS), myocardial infarction (presence or absence according to notes in chart/WebCIS), peripheral vascular disease (presence or absence *as* defined by previous amputation or angiogram/NIFS/carotid doppler results available on WebCIS), prior revascularization procedure including CABG/PTCA/stenting (yes or no), history of left ventricular hypertrophy (presence or absence based on the *pre-initiation of hemodialysis* echocardiogram within 90 days prior to start of hemodialysis), regular use of epogen every 1-2 weeks for at least 3 months (yes or no), use of a beta-blocker at home (yes or no), use of an ACE-inhibitor at home (yes or no), use of an angiotensin receptor blocker at home (yes or no), use of a vasodilator at home (yes or no), use of an alpha-blocker at home (yes or no), use of a calcium channel blocker at home (yes or no). Data on continuous variables will be collected within the three days prior to initiation of hemodialysis, with preference given to

values closest to the start of hemodialysis. These variables include age, body mass index, serum albumin, serum homocysteine level, serum hemoglobin level, serum calcium level, serum phosphate level, serum calcium-phosphate product, serum parathyroid hormone (PTH) level, serum LDL level, serum HDL level, glomerular filtration rate (GFR), right ventricular systolic pressure (RVSP) (based on the *pre-initiation of hemodialysis* echocardiogram within 90 days prior to start of hemodialysis), and mean dialysis time per week.

Part I of the study will seek to determine which of the above variables (if any) are significantly associated with the change in ejection fraction over 1 year (the primary outcome). Part II of the study divides the cohort into two groups, cases and controls. Cases comprise any subject who develops one, or more than one, adverse cardiovascular outcome following 6 months of hemodialysis, *as* defined by the composite cardiovascular endpoint described above (death from any cause, hospitalizations for angina, unstable angina, MI, or CHF, or any coronary revascularization procedure). Controls include any subject who does not develop one of the above adverse outcomes. Part II of the study will examine whether there is a statistically significant difference between the change in ejection fraction over 1 year in patients who manifest adverse cardiovascular outcomes (cases) vs. those who do not (controls).

Analysis: The primary outcome is mean change in left ventricular ejection fraction after 1 year of hemodialysis. Therefore, a paired student t-test, where each subject is their own control, was used to determine power, *as* described below. Part I of the study will seek to determine which of the baseline factors (if any) is significantly associated with the change in ejection fraction ($p<0.05$). For dichotomous variables such as gender (male vs. female), an unpaired student t-test comparing 2 groups will be used. For categorical variables with more than 2 groups, such as race or ethnic group, an ANOVA test will be used. For continuous variables such as age, a linear correlation will be used. Because change in ejection fraction is a continuous outcome, a multiple regression analysis will then be used to determine which baseline characteristics are independent predictors of the primary endpoint. The secondary outcome is a composite endpoint of cardiovascular morbidity and mortality *as* defined above. Part II of the study uses a case-control paradigm to look at change in ejection fraction amongst those subjects with adverse cardiovascular outcomes vs. those subjects without adverse cardiovascular outcomes. An unpaired student t-test will be used to look for a statistically significant difference between the two groups ($p<0.05$). Because the case-control paradigm represents a categorical outcome, the final statistical analysis will be a logistic regression analysis that adjusts for all of the baseline characteristics mentioned above in an attempt to find an independent association between change in ejection fraction and the secondary endpoint.

Sample Size: Given the fact that the primary outcome looks at each subject's change in ejection fraction individually over 1 year, a paired student t-test (which views each subject as their own control) was used to calculate power. The smallest difference of clinical interest was taken to be a change in ejection fraction of absolute value 10% (ex. change in ejection fraction from 30% at baseline to 40% at 1 year). The standard deviation was taken to be absolute value 10%. These values were based upon the clinical opinion of nephrologists and cardiologists at Columbia University Medical Center regarding what represents an important effect size and margin of error when comparing serial transthoracic echocardiograms. Approximately 10 patients are needed to achieve a power of 80% by the above calculation. There was no published data available in the medical literature to determine power in an alternate way.

C. Study Procedure

As this is a retrospective study, the only procedures used were those that were required *as* part of the subjects' clinical management, including hemodialysis. In terms of duration of the study, it will likely take several months to collect all of the data as outlined above and to perform the statistical analyses.

D. Study Drugs

Not applicable

E. Medical Device

F. Location of the Study

This is a retrospective study utilizing data fionspatients cared for at Columbia University Medical Center in New York City, New York There are no additional participating institutions.

G. Potential Risks

There are no potential risks *as* this is a retrospective study. Past interventions, which were not part of this study design, were performed only in the best interest of the patient.

K. Potential Benefits

As this is a retrospective study, the subjects will not directly benefit, however society, including future patients with chronic kidney disease, may definitely stand to benefit. If this study can demonstrate that hemodialysis leads to an improvement in left ventricular ejection fraction in ESRD patients with left ventricular dysfunction, and that this improvement is associated with fewer adverse cardiovascular outcomes in populations characterized by certain baseline characteristics, this may be an argument to initiate hemodialysis earlier in a patient with significant LV dysfunction who has not yet met other criteria for initiating hemodialysis, and who may have a GFR that has not yet dropped below 15, with the hope of decreasing cardiovascular morbidity and mortality.

H. Alternative Therapies

Not applicable

I. Compensation to Subjects:

Not applicable

J. Costs to Subjects

Not applicable

K. Minors as Research Subjects

Not applicable

L. Radiation or Radioactive Substances

Not applicable

M. References

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