The Administration of Subcutaneous Erythropoietin in Elderly Patients with Heart Failure and Normal Ejection Fraction over Three Months is Safe and Effective.

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Background

- Anemia is a significant co-morbidity among patients with heart failure and a normal ejection fraction (HFNEF), commonly called "diastolic heart failure" (DHF).
- Data in subjects with HFNEF are emerging to suggest a relationship between anemia, clinical symptoms, left ventricular structure, hemodynamics, morbidity, and renal function.
- In hospitalized patients with HFNEF, >50% are anemic with a mean hemoglobin of 11.8 ± 2.2 g/dL (*JACC*. 2004; 43: 1432 – 38).
- To date, little is known about the safety and efficacy of subcutaneous erythropoietin injection in the subset of elderly patients with HFNEF and anemia**.**

Methods

- **Study Design**
  - Open label, prospective experimental study over three months
- **Study Subjects**
- ***Inclusion Criteria***
  - Anemia
    - All patients met criteria for anemia defined as hemoglobin < 12 g/dL
  - Heart Failure and a Normal Ejection Fraction (HFNEF)
    - All patients in the HFNEF group met criteria for *diastolic heart failure* as defined by the European Society of Cardiology: signs and symptoms of congestive heart failure, a normal LV ejection fraction (we specifically required ejection fraction ≥50% by three dimensional echocardiography) and evidence of abnormal diastolic function
    - NHANES criteria were employed to define the signs and symptoms of heart failure which include symptoms of dyspnea, resting heart rate, rales, JVD, and evidence of fluid on chest x-ray. Patients met criteria with NHANES score of ≥ 3
- ***Exclusion Criteria***
  - Anemia from known GI blood loss
  - Infiltrative cardiac disease such as hemochromatosis and amyloidosis
  - Hypertrophic Cardiomyopathy
  - Chronic Pulmonary Disease (FEV_1< 60% Predicted)
  - History of DVT or PE within 12 months of study entry
  - Known hypercoagulable state
  - History of stroke or TIA within 6 months of study entry
  - Allergy to human serum albumin or mammalian cell derived products
  - History of Acute Coronary Syndrome within 6 months of study entry
- ***Intervention***
  - Weekly subcutaneous erythropoietin injections were administered to each study participant over a three month period .
  - Supplemental oral ferrous sulfate was administered to all patients.
  - Weekly hemoglobin levels were measured and erythropoietin dosing was adjusted based on a dosing algorithm designed for use in this study not to exceed a rate of rise of hemoglobin of 0.4 g/dL per week.

Endpoints of Study

Multiple physiological endpoints were measured at baseline and follow up. These endpoints included:

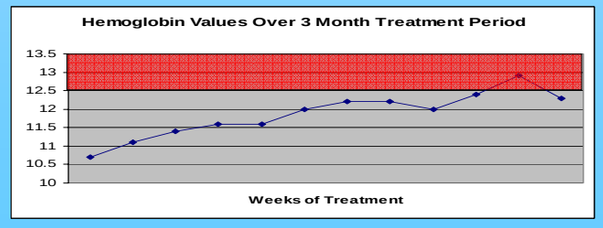
1. Primary Endpoint: Exercise Capacity as measured by
   - ***6 Minute Walk Test***
   - ***Bicycle Ergometer Cardiopulmonary Exercise Testing***
2. Secondary Endpoints:
   - ***Three Dimensional Echocardiography: LV Volumes and Mass***
   - ***Blood Volume Analysis of Plasma Volume by Tagged Albumin Method***
   - ***Quality of Life Measures by Kansas City Cardiomyopathy Questionnaire***

- ***Statistical Analysis***
  - Differences between baseline and treatment were evaluated by paired Student's t test.
  - A p <=0.05 was considered significant.

Baseline Characteristics

Parameter (n=11)	Value
Age (years)	68 ± 10
Percent Female	91%
Race (W, B, H, O)	36% Black 64% Hispanic
BMI (kg/m²)	35 ± 5
Percent Diabetic	73%
Percent CAD	73%
Creatinine (mg/dL)	1.4 ± 0.6
Estimated GFR (mL/min)	59 ± 22

Results



	Baseline (n=10)	Follow Up (n=10)
Adverse Events	N/A	0
Hemoglobin (g/dL)	10.8 ± 0.9	12.2 ± 0.9*
Blood Pressure Parameters (mmHg)		
Systolic Blood Pressure	144 ± 18	134 ± 21
Diastolic Blood Pressure	69 ± 13	64 ± 9*
Mean Arterial Pressure	94 ± 13	88 ± 8
Pulse Pressure	75 ± 15	70 ± 26
Medication Use (no. pts (%))		
Loop Diuretic	5(56)	6(67)
Thiazide	3 (33)	2 (22)
ACE Inhibitor	7 (78)	7 (78)
Beta Blocker	6 (67)	6 (67)
Calcium Channel Blocker	6 (67)	7 (78)
Brain Type Natriuretic Peptide (pg/mL)	187 ± 128	133 ± 119
Plasma Volume (mL)	2865 ± 532	2866 ± 600
Red Cell Volume (mL)	1169 ± 169	1735 ± 350*
Six Minute Walk Test (m)	289 ± 81	321 ± 69*
Bicycle Ergometer Exercise Time (s)	434 ± 196	583 ± 193*
VO2 (mL/min)	628 ± 170	774 ± 260*
VO2 (mL/kg/min)	8.5 ± 2.3	9.4 ± 2*
Peak Exercise HR (bpm)	96 ± 20	110 ± 18
EDV (mL)	109 ± 11	100 ± 10*
LV Mass (g)	174 ± 25	168 ± 22

Limitations

- Single center, uncontrolled, un-blinded clinical trial.

Conclusions

- Erythropoietin administration dosed to effect a rate of rise of <4 gm/dL to elderly anemic patients with HFNEF is associated with significant increases in hemoglobin and red cell volume, without any adverse effect on systemic blood pressure if appropriately followed and treated.
- Prelminary data suggests that such therapy is associated with significant improvement in submaximal exercise capacity, and significant reduction in left ventricular end diastolic volumes.