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 (LICC. 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, races, 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 (FEV1 < 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 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

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

Results

Hemoglobin Values Over 3 Month Treatment Period

<table>
<thead>
<tr>
<th>Weeks of Treatment</th>
<th>Hemoglobin Values (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.8 ± 0.9</td>
</tr>
<tr>
<td>3</td>
<td>12.5 ± 0.9</td>
</tr>
<tr>
<td>6</td>
<td>11.5 ± 0.9</td>
</tr>
<tr>
<td>9</td>
<td>10.5 ± 0.9</td>
</tr>
<tr>
<td>12</td>
<td>10.0 ± 0.9</td>
</tr>
</tbody>
</table>

Adverse Events

Baseline (n=10) Follow Up (n=10)

- Hemoglobin (g/dL)
  - Baseline: 10.8 ± 0.9
  - Follow Up: 12.2 ± 0.9
- Blood Pressure Parameters (mmHg)
  - Systolic Blood Pressure: 144 ± 18
  - Diastolic Blood Pressure: 69 ± 13
  - Mean Arterial Pressure: 94 ± 13
- Pulse Pressure: 75 ± 15
- Medication Use (no. pts (%))
  - Loop Diuretic: 5 (56)
  - ACE Inhibitor: 7 (78)
  - Beta Blocker: 6 (67)
  - Calcium Channel Blocker: 6 (67)

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.
- Preliminary data suggests that such therapy is associated with significant improvement in submaximal exercise capacity, and significant reduction in left ventricular end diastolic volumes.

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