Intermittent inotropic infusions for the treatment of refractory end stage heart failure: a randomized clinical study


3rd Cardiology Dept. University of Athens, Medical School
Introduction

The steady worldwide increase in prevalence of heart failure represents a major health concern.

Despite the progress made in pharmacological therapy (β-blockers, ACE-I, Spironolactone), the prognosis of patients with advanced heart failure remains poor.

Therapeutic options

- CRT-ICD
- Htx
- Chronic mechanical circulatory support
  - Bridge to transplantation
  - Bridge to recovery
  - Destination therapy
- Intermittent inotrope infusion?
Chronic intermittent dobutamine infusion and mortality

Els 1998 (Israel)

Erlemeier 1992 (Germany)

DICE Collaborative Group 1997 (Italy)

Dies 1986 (USA)

Pooled fixed effects

Pooled random effects

Pooled Fixed Effects = 1.561895 (95% CI = 0.713053 to 3.490343)

Pooled Random Effects = 1.49885 (95% CI = 0.51848 to 3.923562)
Long-term Intermittent Dobutamine Infusion, Combined With Oral Amiodarone for End-Stage Heart Failure*

A Randomized Double-Blind Study

John N. Nanas, MD; Eleftheria P. Tsagalou, MD; John Kanakakis, MD; Serafim N. Nanas, MD; John V. Terrovitis, MD; Thomas Moon, PhD; and Maria I. Anastasiou-Nana, MD

*JN Nanas et al, Chest 2004
Levosimendan is a novel inotropic agent with unique pharmacologic properties
- increase the calcium sensitivity (calcium sensitizer).
- Vasodilatory properties

In acute decompensated heart failure patients, refractory to therapy with dobutamine, simultaneous infusion of levosimendan improved hemodynamics

*Nanas et al. Am J Cardiol 2004*
In this randomized study, we compared the safety and efficacy of intermittent intravenous infusions of levosimendan and dobutamine, administered alone or in combination, in patients treated with amiodarone, who presented with decompensated refractory end-stage heart failure.

**Aim**

Survival free from death or emergency LVAD implantation at 6 months, was the primary end point of the study.
63 patients with decompensated end stage heart failure refractory to standard therapy, admitted to the hospital

24 - 72 hr continuous dobutamine infusion

Stabilization

Randomization

ILI Group, (n=21)
ILI (6 h/ week for 6 mo) + 400 mg Amiodarone/day

IDI Group, (n=21)
IDI (6 h/ week for 6 mo) + 400 mg Amiodarone/day

ILDI Group, (n=21)
ILD (6 h/ week for 6 mo) + 400 mg Amiodarone/day

ILI: Intermittent Levosimendan Infusion (0.3 μg/kg/min)
IDI: Intermittent Dobutamine Infusion (10 μg/kg/min)
ILDI: Intermittent Levosimendan (0.2 μg/kg/min) + Dobutamine Infusion (10 μg/kg/min)
Methods (II)

Clinical, hemodynamic and laboratory parameters recorded at the entrance of the patients in III and after 3 months

- Systolic arterial blood pressure
- Pulmonary Capillary Wedge Pressure
- Cardiac Index
- Mean Pulmonary Arterial Pressure
- Serum Creatinine
- Serum Sodium
- Hemoglobin
- Left Ventricle Ejection Fraction
## Results (I)
### Patients baseline characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>IDI</th>
<th>ILI</th>
<th>ILDI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (v)</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>ICM(%)/IDC(%)</td>
<td>11/10</td>
<td>10/11</td>
<td>11/10</td>
<td>NS</td>
</tr>
<tr>
<td>Men/Women</td>
<td>20/1</td>
<td>20/1</td>
<td>19/2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (Y)</td>
<td>53±13</td>
<td>55±12</td>
<td>61±11</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA (class)</td>
<td>4±0</td>
<td>4±0</td>
<td>4±0</td>
<td>NS</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>102±13</td>
<td>101±9</td>
<td>95±9</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>21±5</td>
<td>23±7</td>
<td>24±6</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>31±9</td>
<td>26±7</td>
<td>28±7</td>
<td>NS</td>
</tr>
<tr>
<td>CI(L/min/m2)</td>
<td>1.7±0.4</td>
<td>1.6±0.3</td>
<td>1.8±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Na (mEq/l)</td>
<td>135±5</td>
<td>137±5</td>
<td>134±7</td>
<td>NS</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>1.4±0.5</td>
<td>1.6±0.6</td>
<td>2.0±0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Furosemide/d(mg)</td>
<td>408±218</td>
<td>410±118</td>
<td>345±120</td>
<td>NS</td>
</tr>
</tbody>
</table>

IDCM: Idiopathic Dilated, ICM: Ischemic Cardiomyopathy, CI: Cardiac Index, LVEF: Left Ventricle Ejection Fraction, PCWP: Pulmonary Capillary Wedge Pressure, SAP: Systolic Arterial Pressure, NYHA: New York Heart Association Class, Na: Serum Sodium, Cr: Serum Creatinine

ILI: Intermittent Levosimendan Infusion (0.3 μg/kg/min)
IDI: Intermittent Dobutamine Infusion (10 μg/kg/min)
ILDI: Intermittent Levosimendan (0.2μg/kg/min) + Dobutamine Infusion (10 μg/kg/min)
Results (III)

Event = Death + Urgent LV AD implantation

- Levosimendan
- Dobutamine
- Levosimendan plus Dobutamine

Levosimendan vs Dobutamine, p=0.037
Levosimendan vs Levosimendan plus Dobutamine, p=0.009
## Results (II)

### Changes in functional and hemodynamic parameters 3mo after study treatment onset

<table>
<thead>
<tr>
<th></th>
<th>NYHA</th>
<th>PCWP</th>
<th>MPAP</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILI Baseline</td>
<td>4.0±0</td>
<td>27±4</td>
<td>41±6</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>3 mo</td>
<td>2.8±1.0</td>
<td>19±8</td>
<td>30±7</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td>IDI Baseline</td>
<td>4.0±0</td>
<td>30±7</td>
<td>43±10</td>
<td>1.8±0.5</td>
</tr>
<tr>
<td>3 mo</td>
<td>2.7±0.8</td>
<td>24±9</td>
<td>37±10</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>ILDI Baseline</td>
<td>4.0±0</td>
<td>27±6</td>
<td>44±9</td>
<td>1.8±0.4</td>
</tr>
<tr>
<td>3 mo</td>
<td>2.7±0.8</td>
<td>23±13</td>
<td>39±15</td>
<td>1.8±0.4</td>
</tr>
</tbody>
</table>

ILI: Intermittent Levosimendan Infusion (0.3 \( \mu \text{g/kg/min} \))
IDI: Intermittent Dobutamine Infusion (10 \( \mu \text{g/kg/min} \))
ILDI: Intermittent Levosimendan (0.2\( \mu \text{g/kg/min} \)) + Dobutamine Infusion (10 \( \mu \text{g/kg/min} \))
**Results(IV)**

Modes of “death”, hospitalization, urgent and total LVAD implantation rates at 6 months of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Dobutamine (n=21)</th>
<th>Levosimendan (n=21)</th>
<th>Dobutamine + levosimendan (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modes of death (% of deaths)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Progressive pump failure</td>
<td>60</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>• Sudden cardiac</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>LVADs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Urgent left ventricular assist device implantation</td>
<td>14.3</td>
<td>0</td>
<td>14.3</td>
</tr>
<tr>
<td>• Total left ventricular assist device implantation</td>
<td>14.3</td>
<td>24.0</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Hospitalizations</strong></td>
<td>37</td>
<td>53</td>
<td>35</td>
</tr>
</tbody>
</table>

*Values are % of patients in the corresponding group
Conclusion

• In patients with end-stage heart failure, refractory to standard medical therapy, the intermittent infusion of Levosimendan improved the outcome in comparison to the Intermittent infusion of Dobutamine or Levosimendan plus dobutamine.

• These results suggest an adverse effect of dobutamine, when added to levosimendan, in these patients.