

SAFETY AND EFFICACY OF SIX-MONTH OUTPATIENT INTERMITTENT NESIRITIDE INFUSIONS

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ABSTRACT

Background: In patients with acutely decompensated heart failure (HF), intravenous infusion of nesiritide improves hemodynamics and symptoms with few adverse effects. We investigated the tolerability as well as efficacy of outpatient intermittent infusions of nesiritide.

Methods: Patients with severe chronic HF who were unresponsive to treatment with standard therapies were included. They received intermittent intravenous nesiritide (2 mcg/kg bolus dose followed by 0.01 mcg/kg/min over 4-6 hours) and were followed for 6 months for changes in NYHA class function, hospitalization for worsening of HF symptoms, frequency of visits to the HF clinic, cardiac index (CI), cardiac output (CO), and any possible side effects.

Results: Forty patients (27 were males, with a mean age of 68 ± 14 years) were included. At the beginning of the study, 34 patients were in NYHA class III, 5 patients in class II, and 1 patient in class IV. At the end of study 16 had improvement in their class function ($p=0.0037$), 22 remained in the same class, and 2 patients regressed. The total number of hospitalizations in the 6 month period prior to therapy was 42, which declined to 31 during the 6 months following initiation of therapy ($p=0.1735$). The number of visits to the HF clinic declined from an average of 3.75 ± 0.95 visits/month to an average of 2.53 ± 1.18 visits/month ($p<0.0001$). Baseline CI was 2.77 ± 0.76 L/min/m² (mean \pm SD) increased to 2.98 ± 0.91 L/min/m² ($p=0.4717$). On the other hand, CO increased from 5.60 ± 1.92 L/min (mean \pm SD) to 6.0 ± 2.06 L/min ($p=0.4999$). Therapy was well tolerated by most patients. Symptomatic hypotension was observed in two patients.

Conclusion: These results suggest that the use of nesiritide in end-stage HF patients refractory to standard medical treatment in an outpatient setting improves NYHA class function, and frequency of visits to the HF clinic, but not hospitalization for worsening HF or cardiac function.

Keywords: Chronic decompensated heart failure, Nesiritide, Outpatient, CHF clinics

INTRODUCTION

Heart failure (HF) has become a major health problem that affects approximately 5 million patients in the United States ¹. The economic and human impact of this disease on the health system continues to rise despite adoption of evidence-based pharmacotherapy with proven mortality and morbidity benefits. Patients with symptomatic HF who are at high risk for repeated admissions, chronic decompensated HF, are left with few therapeutic options and outpatient care through HF clinics becomes vital in the management of their symptoms.

Nesiritide (Natrecor®), a human B-type natriuretic peptide, is a potent vasodilator that reduces both preload and afterload and has additional diuretic and natriuretic properties. It was approved for the intravenous treatment of patients with acutely decompensated HF who have dyspnea at rest or with minimal activity. The approval of the drug was based on studies showing hemodynamic benefits of nesiritide in patients with decompensated HF ^{2,3}. Other studies show improvement in hemodynamic parameters in HF patients who are not decompensated ⁴.

A novel approach to improve quality of life in patients with chronic decompensated heart failure despite optimal oral drug therapy is to use nesiritide in the outpatient setting. Despite the lack of data definitively supporting nesiritide's use in the outpatient setting, early results from few trials have supported the safety and efficacy of outpatient nesiritide serial infusions in this group of patients ⁵⁻⁸.

The objective of this study was to assess the tolerability as well as effects of periodic outpatient administration of nesiritide in patients with chronic decompensated HF who were receiving appropriate medical therapy but remained at risk for recurrent hospitalization. We assessed the effect of nesiritide on improving functional status assessed by the New York Heart Association (NYHA) functional class, reducing hospitalization for worsening HF, and reducing the number of visits to the HF center. In addition, we studied the long-term effect of nesiritide on cardiac function assessed by measuring cardiac output (CO) and cardiac index (CI).

MATERIALS AND METHODS

We conducted a single-center, non-randomized, open-label, prospective study on patients with chronic left ventricular systolic dysfunction. All the patients were eighteen years of age or older and had refractory symptoms or had ≥ 2 hospital admissions for acutely decompensated HF within the preceding 6 months. Patients receiving maximal oral therapy with, diuretics, angiotensin converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARBs), or hydralazine-isosorbide dinitrate combination, beta blockers, nitrates, and spironolactone, unless intolerance was documented, were included in the study. Patients were considered refractory to drug therapy if they continued to have symptoms of heart failure despite maximal medical therapy. We excluded patients with renal insufficiency, myocardial infarction in the preceding 30 days, had undergone a placement of a biventricular pacemaker, or if they had systolic blood pressure consistently less than 90 mm Hg. Written informed consent was obtained from each patient.

At each visit to the cardiac infusion unit, patients received nesiritide intermittent infusions at a dose of 2 mcg/kg bolus followed by 0.01 mcg/kg/min over 4-6 hours. Individual assessments were performed and included detailed physical examination, blood analysis and comprehensive education and counseling. Diuretics were given at each session as required, depending on clinical signs and body weight. Potassium and magnesium supplements were adjusted according to serum levels. At the beginning of the study treatment was administered either one or two times a week for a 4-6 hour period depending on symptoms. Subsequently, patients who experienced improvement in symptoms received nesiritide infusions less frequently. Inotropes therapy was not used unless it was believed to be required by the treating physician.

All patients were followed for 6 months after nesiritide therapy for changes in NYHA class function, hospitalization for worsening of HF symptoms, frequency of visits to the HF clinic, CI, CO, and any possible side effect due to nesiritide. We compared hospitalization for worsening HF and frequency of visits to the heart failure center to the 6-month period prior to therapy. Hospitalization for

worsening HF was defined as an episode of clinical worsening of preexisting heart failure requiring more than 24-hour hospital stay and intravenous infusion of inotropes, and/or furosemide, and/or nesiritide.

We used the wilcoxon signed rank test to compare improvement in NYHA class. Student's t-test was used to compare the number of visits to the heart failure center, as well as any changes in CI/CO before and after therapy.

RESULTS

Forty patients (27 were males, with a mean age of 68 ± 14 years) were included in the study. The primary etiologic causes for HF were ischemic (28 patients), idiopathic (11 patients), and viral cardiomyopathy (1 patient).

NYHA class function

At the beginning of the study, 34 patients were in NYHA class III, 5 patients in class II, and 1 patient in class IV. After 6 months of treatment with nesiritide, 22 patients were in class III, 18 patients in class II, and none in class IV. Of the 40 patients, 16 had improvement in their NYHA class function ($p=0.0037$), 22 remained in the same class, and 2 patients regressed

Hospitalization

The total number of hospitalizations due to HF exacerbation in the 6 month period prior to nesiritide therapy was 42, which declined to 31 during the 6 months following the initiation of nesiritide therapy ($p=0.1735$).

Frequency of visits to the HF clinic

The number of visits to the HF infusion clinic for all patients declined from an average of 3.75 ± 0.95 visits/month before treatment with nesiritide to an average of 2.53 ± 1.18 visits/month at the end of the study ($p<0.0001$).

Cardiac Index / Cardiac Output

At the beginning of the study mean CI was 2.77 ± 0.76 L/min/m² (mean \pm SD) and increased after 6 months of nesiritide treatment to 2.98 ± 0.91 L/min/m² ($p=0.4717$). On the other hand, CO increased from 5.60 ± 1.92 L/min (mean \pm SD) to 6.0 ± 2.06 L/min ($p=0.4999$) at the end of the study.

Tolerability

The intermittent administration of nesiritide was well tolerated by most patients throughout the study period. Symptomatic hypotension was observed in two patients which necessitated omitting the bolus dose during subsequent visits.

DISCUSSION

Patients with HF who are on maximally tolerated drug therapy and remain chronically decompensated are frequently hospitalized and have a poor quality of life. There is a big need to offer treatment regimens for such patients that are less invasive than ventricular replacement strategies, offer more hope in terms of survival, and perhaps are more effective than chronic inotropic therapy or hospice care. Nesiritide lacks inotropic and proarrhythmic effects which makes it attractive agent for evaluation as treatment of chronic decompensated HF. A number of small studies in the past few years have indicated improvement in symptoms and even fewer hospitalizations when intermittent infusion of nesiritide was used⁵⁻⁸.

In this study, patients were on quite appropriate standard medical therapy. Fifty percent of patients were on ACEIs and 32.5% were on ARBs; thus 82.5% of patients were receiving blockers of the renin-angiotensin-aldosterone system. Beta-blocker use was at 77.5%, diuretic use at 97.5%, and aldosterone antagonist use at 22.5%.

In our study more than 600 infusions of nesiritide were administered and more than 99% were completed and well tolerated. Only two patients developed symptomatic hypotension which necessitated giving the continuous infusion of the drug without the bolus dose during subsequent visits without adverse

effects. Nesiritide use in the outpatient setting does appear practical. The drug is relatively easy to store, dose, and administer. A significant amount of drug can be given in just a few hours, and the adverse effect profile is acceptable. No titration is required and monitoring is minimal after the first hour.

None of the patients received an inotropic agent during a study visit because of clinical evidence of decompensated HF and none of the patients died during the study period. This inotrope sparing effect of nesiritide could be of clinical importance since the commonly used agents, dobutamine and milrinone, increase the incidence of both atrial and ventricular arrhythmias^{9,10}.

During the 6-month intermittent nesiritide therapy 40% of patients had improvement in their NYHA class function, 55% were stabilized while 5% regressed. This was translated into a significantly fewer number of visits to the HF clinic as well as fewer hospitalizations due to HF exacerbation, a number that did not reach statistical significance. Our results are in agreement with the recently published study, the Follow-Up Serial Infusions of Nesiritide in Advanced Heart Failure (FUSION II), which suggests that the outpatient periodic administration of nesiritide in advanced chronic heart failure had no effect on cardiovascular hospitalization¹¹.

We did not observe a significant difference in CI/CO in this group of patients as compared to baseline. This is expected as nesiritide has no direct inotropic effect and the acute increase in CI/CO in clinical trials was attributed to its effect on other hemodynamic parameters.

Based on these preliminary results, the treatment of chronic decompensated HF patients with intermittent nesiritide infusions in an outpatient disease management setting seems to be a plausible approach likely to be clinically effective. This study was limited by its open-label design, the relatively small number of patients studied, the absence of a comparable group, and absence of long term follow up.

Two meta-analyses have been published that suggest an increased risk of worsening renal function and increased mortality associated with the use of nesiritide^{12,13}. Although these meta-analyses are certainly hypothesis generating, part of the data used in these analysis were pooled from early dosing trials where the doses of nesiritide used were higher than the FDA approved dose. In addition, none of them were powered to look at the effect of nesiritide on renal function or mortality. Moreover, newer studies suggest that there was no evidence of worsening renal function with nesiritide and no signal of an adverse mortality effect^{11,14}.

CONCLUSION

The use of nesiritide in end-stage HF patients refractory to standard medical treatment in an outpatient setting seems to be well tolerated and to improve NYHA class function, and frequency of visits to the HF clinic, but not hospitalization for worsening HF or cardiac function.

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