

Impact of Acute Serum Creatinine Elevation in Patients Treated with Nesiritide

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ABSTRACT

Background: We assessed the effect of increases in serum creatinine on mortality in nesiritide-treated versus control subjects with acute decompensated heart failure (ADHF).

Hypothesis: Mortality effect of nesiritide-related increases in serum creatinine differs from that of standard therapies.

Methods: Scios Inc., granted unrestricted access to data from all 5 randomized, controlled nesiritide infusion trials completed to date in patients hospitalized with ADHF. We used 2 different definitions of acute serum creatinine increase: >0.3 mg/dL and >0.5 mg/dL within 30 days of study enrollment and determined 30-day mortality risk for nesiritide-treated versus control subjects utilizing each definition.

Results: A total of 1,270 subjects participated in the 5 trials. A >0.3 mg/dL increase in serum creatinine was associated with a significant increase in mortality risk in control subjects, (hazard ratio [HR]: 3.47, 95% confidence interval [CI]: 1.49–8.09) but not in nesiritide-treated subjects (HR: 1.65, 95% CI: 0.90–3.05). Results were similar for a >0.5 mg/dL increase (control HR: 5.12, 95% CI: 2.09–12.57 and nesiritide HR: 1.77, 95% CI: 0.90–3.51). In subjects with >0.3 mg/dL and >0.5 mg/dL increases in serum creatinine, respectively, the 30-day mortality odds ratios for nesiritide relative to control were 0.73 (95% CI: 0.29–1.93) and 0.52 (95% CI: 0.17–1.63) using a stratified Mantel-Haenszel analysis.

Conclusions: The impact of increased serum creatinine on mortality was attenuated in nesiritide-treated patients compared to control, suggesting that the mechanism and clinical significance of increases in serum creatinine associated with nesiritide treatment may differ from those associated with standard therapies. Further investigation is warranted.

Introduction

Observational studies have demonstrated a strong association between acute in-hospital increases in serum creatinine and unfavorable outcomes in patients with acute decompensated heart failure (ADHF).^{1–6} A recent selective pooled analysis⁷ has suggested an increased prevalence of serum creatinine increase within 30 days of nesiritide administration in patients hospitalized with ADHF. Based on these data, the hypothesis that nesiritide-associated increases in serum creatinine may affect short-term survival has been advanced, but not tested.⁸ We independently assessed the relationship between an increase in serum creatinine and 30-day mortality in nesiritide-treated versus control subjects.

Methods

A PubMed literature search, limited to the English language, was used to identify completed, randomized, controlled clinical trials evaluating nesiritide infusion in hospitalized patients with ADHF. Six trials with at least 30-day follow-up

were identified. Scios Inc. (Mountain View, CA, USA) sponsored all of these trials. The company agreed to provide a dataset from these trials for independent evaluation. In 1 trial, serum creatinine data were only collected at baseline and at 12 hours after the start of infusion.⁹ Consequently, this trial was excluded from subsequent analysis. The remaining 5 trials comprise the current study population. The methodology and primary results of these trials have been previously published.^{10–13} Table 1 shows the doses as well as durations of infusion in the trials.

The primary analysis examined the impact of an increase in serum creatinine detected within 30 days of study enrollment on 30-day mortality. Arbitrary serum creatinine cut points of >0.3 mg/dL and >0.5 mg/dL were chosen in order to provide results comparable to those in the published literature.^{1,2,4,5,7}

Statistical Analysis

An independent biostatistician provided the statistical analysis. Using SAS version 8 statistical software (SAS Institute, Inc., Cary, NC), 2 types of statistical analyses were conducted. First, Cox's time dependent covariate model was

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Table 1. Nesiritide Trials Included in the Present Analysis

Study	Control	Patients		Nesiritide Dose (mcg/kg/min)	Median (IQR) Duration of Infusion (hours)
		Nesiritide	Control		
Mills et al ¹⁰	Placebo	74	29	0.015, 0.03, or 0.06	24.0 (24.0–24.1)
Efficacy trial ¹²	Placebo	85	42	0.015 or 0.03	24.2 (7.8–47.7)
Comparative trial ¹²	Standard care	203	102	0.015 or 0.03	30.4 (23.0–65.1)
PRECEDENT ¹¹	Dobutamine	163	83	0.015 or 0.03	24.1 (24.0–46.5)
VMAC ¹³	Nitroglycerin\Standard care	273	216	0.01	24.3 (24.0–44.2)

used to estimate the association between serum creatinine increase and survival time within 30 days for each treatment group. For each group, the data from the 5 studies were utilized to calculate the Cox estimate for the hazard ratio (HR) (stratified by study) along with the corresponding 95% confidence intervals (CIs). Then the ratio of these 2 HRs, that is, nesiritide HR/control HR, together with its corresponding 95% CI were calculated. Next, as a secondary “confirmatory” analysis, the subgroups of patients in whom a serum creatinine increase (>0.3 or >0.5mg/dL) was detected within 30 days were considered to construct standard 2 by 2 tables for each of the 5 studies. The exact Mantel-Haenszel technique was then used to combine these tables and the exact 95% CI for the odds ratio between the 2 groups (stratified by study) were calculated. In addition, since there were no deaths in subjects with serum creatinine increase >0.3 mg/dL in the study by Mills et al¹⁰ analyzing the data stratified by study necessitated exclusion of this trial. Therefore, both the Cox and Mantel-Haenszel analyses were repeated using non-stratified models that combined the data on all patients across the 5 studies independent of trial. *P* values of >.05 were considered significant.

Results

A total of 1,270 subjects (798 nesiritide, 472 control) participated in the 5 trials. At baseline, both nesiritide-treated and control groups had similar demographic and clinical characteristics (Table 2). Baseline serum creatinine data were missing in 12 subjects (0.9%). In the remaining subjects, the mean serum creatinine at baseline was 1.6±1.1 mg/dL in nesiritide-treated and 1.6±0.9 mg/dL in control subjects (*p* = 0.946). Overall, 22 subjects (1.7%) were excluded from the mortality analyses due to missing serum creatinine data.

Serum creatinine increases >0.3 mg/dL occurred in 32% (254/786) of nesiritide-treated subjects compared to 23% (107/462) of control subjects (*p* = 0.001). Similarly, serum creatinine increases >0.5 mg/dL occurred in 19% (151/786) of nesiritide-treated and 14% (63/462) of control subjects (*p* = 0.01).

Using the stratified time-dependent Cox model, the 30-day mortality HR associated with a >0.3 mg/dL increase in serum creatinine was 1.65 (95% CI: 0.90–3.05, *p* = 0.103) in nesiritide-treated subjects and 3.47 (95% CI: 1.48–8.09, *p* = 0.004) in control subjects (Figure 1).

With a threshold of >0.3 mg/dL increase in serum creatinine, the increased risk of 30-day mortality associated with increased serum creatinine in nesiritide-treated patients was approximately half the increase in risk of 30-day mortality for control patients (nesiritide versus control: 0.48 [95% CI: 0.16–1.37]). Likewise, the 30-day mortality HR associated with a >0.5 mg/dL increase of serum creatinine was 1.77 (95% CI 0.90–3.15, *p* = 0.101) in nesiritide and 5.12 (95% CI: 2.09–12.57, *p* <0.001) in control subjects. Using a threshold of >0.5 mg/dL increase in serum creatinine, the ratio of the nesiritide-treated HR versus the control HR was 0.35 (95% CI: 0.11–1.09). More simply stated, nesiritide-treated subjects who had an increase in serum creatinine of >0.5 mg/dL experienced only about one-third of the increase in risk that control subjects with a similar rise in serum creatinine experienced.

The non-stratified time-dependent Cox model yielded similar findings. In this model, the 30-day mortality HR associated with a >0.3 mg/dL increase in serum creatinine was 1.76 (95% CI: 0.97–3.18, *p* = 0.063) in nesiritide-treated and 3.10 (95% CI: 1.39–6.93, *p* = 0.006) in control subjects, and the 30-day mortality HR associated with a >0.5 mg/dL increase in serum creatinine was 1.95 (95% CI: 0.99–3.85, *p* = 0.053) in nesiritide-treated and 4.61 (95% CI: 1.97–10.81, *p* <0.001) in control subjects.

Mantel-Haenszel analyses confirmed the Cox findings. For nesiritide-treated versus control subjects with serum creatinine increase >0.3 mg/dL, 30-day mortality rates were 6.7% (17 of 254 subjects) and 9.3% (10 of 107 subjects), respectively (*p* = 0.39; Figure 2). In these subjects, the point estimate of 30-day mortality odds ratio for nesiritide relative to control in subjects with a serum creatinine increase >0.3 mg/dL was 0.73 (95% CI: 0.29–1.93) when the data were analyzed stratified by study, and 0.70 (95% CI: 0.29–1.77) when the data from all subjects were grouped together (i.e.,

Table 2. Demographic and Clinical Characteristics at Baseline

	Nesiritide (n = 798)	Control (n = 472)	P-value
Age (yr), mean±SD	61.4±13.4	61.3±14.0	0.845
Male gender, n(%)	567 (71)	318 (67)	0.185
African American, n (%)	202 (25)	115 (24)	0.737
New York Heart Association class, n (%)			0.550
I	2 (<1)	2 (<1)	
II	40 (5)	30 (6)	
III	435 (55)	249 (53)	
IV	300 (38)	173 (37)	
New onset heart failure	21 (3)	18 (4)	
Weight (kg), mean±SD*	81±21	83±23	0.164
Systolic blood pressure (mm Hg), mean±SD†	120.3±22.6	120.6±20.3	0.823
Serum creatinine (mg/dL), mean±SD‡	1.6±0.9	1.6±1.1	0.946
Creatinine clearance (mL/min), mean±SD§	69.1±40.0	70.2±44.7	0.630
Left ventricular ejection fraction (%),mean±SD	24.8±11.8	25.5±13.5	0.540

SD, standard deviation; *N for control and nesiritide groups are 470 and 796, respectively; †N for control and nesiritide groups are 470 and 786, respectively; ‡N for control and nesiritide groups are 467 and 791, respectively; §Calculated using Cockcroft-Gault equation. N for control and nesiritide groups are 465 and 788, respectively; ||N for control and nesiritide groups are 256 and 399, respectively. The Comparative trial¹² and PRECEDENT¹¹ did not collect left ventricular ejection fraction data.

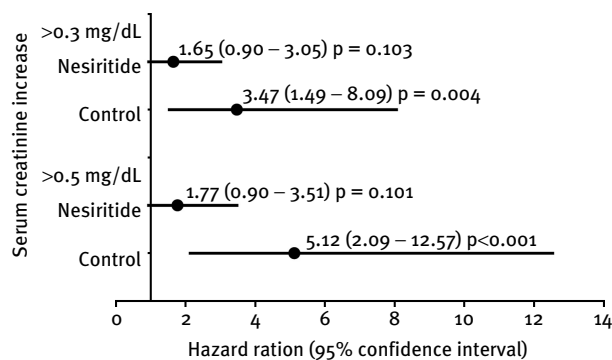


Figure 1. Time-dependent 30-day mortality hazard ratios (HR) associated with serum creatinine elevations of >0.3 mg/dL and >0.5 mg/dL relative to subjects without the indicated serum creatinine elevation in nesiritide and control groups. Lines depict 95% confidence intervals.

non-stratified). Likewise, for nesiritide-treated and control subjects with serum creatinine increase >0.5 mg/dL, the 30-day mortality rates were 7.3% (11 of 151 subjects) and 12.7% (8 of 63 subjects), respectively ($p = 0.29$; Figure 2). In these subjects, the point estimates for the 30-day mortality odds ratios for nesiritide-treated relative to control subjects were 0.52 (95% CI: 0.17–1.63) stratified by study, and 0.54

(95% CI: 0.19–1.64) grouped together. In comparison, the 30-day mortality rates in nesiritide and control subjects who did not have a >0.5 mg/dL increase in serum creatinine were 5.8% (37 of 635 subjects) and 4.3% (17 of 399 subjects), respectively ($p = 0.32$); similar results were obtained using a >0.3 mg/dL threshold (data not shown).

Discussion

Our analysis confirms the results of previous studies, demonstrating an increase in short-term mortality risk in hospitalized ADHF patients who develop an acute increase in serum creatinine.^{1–6} However, our data show that this risk varied significantly according to the treatment the patients received. In the 5 trials included in our analysis, increases in serum creatinine had a highly significant impact on short-term mortality in control subjects; however this impact was attenuated in nesiritide-treated subjects. The 30-day mortality odds ratio for nesiritide-treated relative to control in subjects who developed an acute increase in serum creatinine ranged from 0.52 to 0.73 depending upon the threshold chosen to define an acute increase in serum creatinine, the statistical model employed, and the mortality effect associated with an acute increase achieved statistical significance only in control subjects. Since changes in renal

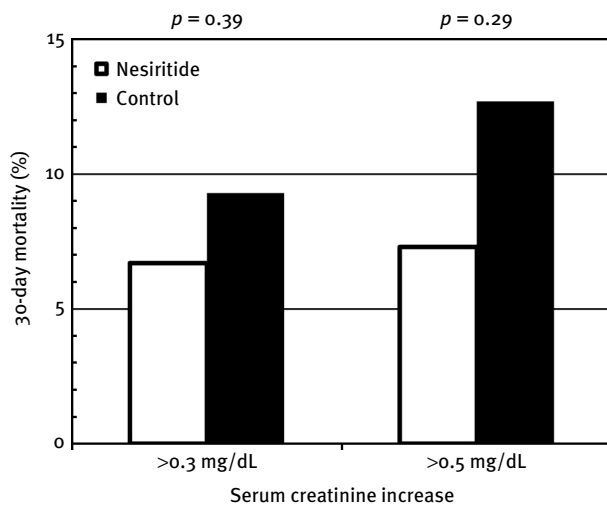


Figure 2. Thirty-day mortality in nesiritide and control subjects with serum creatinine elevations of >0.3 mg/dL and >0.5 mg/dL.

function associated with nesiritide treatment appeared to have a lesser impact on short-term mortality, our findings raise questions about an independent relationship between nesiritide-associated increases in serum creatinine and increased mortality.

Increases in serum creatinine in the nesiritide-treated patients may be due to a different mechanism from that operating in control patients. B-type natriuretic peptide and nesiritide (human recombinant BNP) have potent angiotensin and aldosterone blocking properties.^{12,14,15} Previous studies have demonstrated early elevation in serum creatinine with the use of other angiotensin or aldosterone blocking agents.¹⁶ Neurohormonal blockade not only reduces mean arterial pressure, it also dilates efferent arterioles, reducing glomerular filtration rate (GFR) and thus leading to an increase in serum creatinine.¹⁶ This effect is enhanced in patients with chronic renal insufficiency, since these patients are more dependent on elevated intraglomerular pressure for renal function.^{16,17} However, the increase in serum creatinine seen with angiotensin and aldosterone blocking agents has been associated with better, rather than worse, clinical outcomes.^{16,17} The hypothesis that a similar neurohormonal mechanism may be involved in the explanation of our findings seems worthy of further exploration.

These data have several limitations. This was a retrospective analysis of pooled data. Because the individual studies were neither designed nor powered to assess mortality or changes in renal function, pooled analyses were required. These analyses are limited by the heterogeneity of the studies being pooled. The dose and duration of the nesiritide infusion, the type of control group employed (placebo or

active control), and the sampling criteria used for assessing serum creatinine values varied between the 5 studies. In addition, the type, dose, and duration of concomitant medications that the subjects received during the 30-day post-randomization period assessed in this evaluation are unknown. Differences in concomitant medication exposure may have influenced both the development of increases in serum creatinine and the risk associated with this development. In addition, reflecting the small number of deaths in these trials, the 95% CIs on the point estimates of the mortality odds and HRs are large, even when the 5 studies are combined and this inhibited our ability to demonstrate statistically significant differences between treatment groups. These limitations highlight the need for prospective randomized studies to confirm the hypothesis generated by results of the current study.

Conclusions

Our data confirm an association between nesiritide administration and an increased risk of acute serum creatinine increases within 30 days of treatment in patients hospitalized with ADHF. However, 30-day mortality odds ratios and HRs were substantially lower in nesiritide-treated subjects who experienced serum creatinine increases as compared to control subjects who had similar changes in serum creatinine. These observations suggest that nesiritide-related serum creatinine elevation may not be associated with as severe an adverse impact on mortality as similar increases in patients who did not receive nesiritide. We hypothesize that this difference may be related to the known neurohormonal blocking effects of nesiritide.

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