Long-term Outcome of Patients Treated With Prophylactic Nesiritide for the Prevention of Acute Kidney Injury Following Cardiovascular Surgery

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ABSTRACT

Background: Previously, we reported that the prophylactic use of nesiritide did not reduce the incidence of dialysis or death following cardiovascular (CV) surgery despite reducing the incidence of acute kidney injury (AKI) in the immediate postoperative period. Therefore, we investigated whether the observed renal benefits of nesiritide had any long-term impact on cumulative patient survival and renal outcomes.

Methods: Participants of the Nesiritide Study, a previously reported prospective, double-blind, placebo-controlled, randomized clinical trial investigating the effect of nesiritide on the incidence of dialysis or death at 21 days in adult patients undergoing high-risk CV surgery, were included in the study. Data of the participants' most recent health and renal function status were obtained using institutional review board-approved patient questionnaires, medical records, and the database of the Social Security Administration.

Results: Data on all 94 patients from the Nesiritide Study were obtained. The mean follow-up period was 20.8 $\pm$ 10.4 months. No differences in cumulative survival between the groups were noted at follow-up (nesiritide 77.7% vs placebo 81.6%, $P = 0.798$). Patients with in-hospital incidence of AKI had a higher rate of mortality than those with no AKI (AKI 41.4% vs no AKI 10.7%, $P = 0.002$). However, differences in survival time were not significant between the groups when the analysis was restricted to patients with AKI (nesiritide 16.8 $\pm$ 4 months vs placebo 18.5 $\pm$ 2.3 months, $P = 0.729$).

Conclusions: Renoprotection provided by nesiritide in the immediate postoperative period was not associated with improved long-term survival in patients undergoing high-risk CV surgery.

Introduction

Evidence for the renoprotective effect of natriuretic peptides in clinical settings remains controversial.[1–4] Previously, we reported in a retrospective study that the use of the B-type natriuretic peptide (BNP) nesiritide (Natrecor) in patients with impaired renal function (serum creatinine [SCr] >1 mg/dL) who were undergoing cardiovascular (CV) surgery was associated with a dramatic reduction in 21-day dialysis-free survival (odds ratio [OR]: 0.35, 95% confidence interval [CI]: 0.14–0.87, $P = 0.024$).[5] However, in a follow-up prospective, randomized clinical trial (the Nesiritide Study), we could not demonstrate a benefit for prophylactic use of nesiritide as related to the incidence of 21-day dialysis and/or death in patients undergoing high-risk CV surgery (nesiritide 6.6% vs control 6.1%; $P = 0.914$).[6] The study did demonstrate that the prophylactic use of nesiritide was associated with reduced incidence of acute kidney injury (AKI) as defined by the Acute Kidney Injury Network in the immediate postoperative period (nesiritide 6.6% vs placebo 28.5%, $P = 0.004$) and lower mean SCr (nesiritide 1.18 $\pm$ 0.41 mg/dL vs placebo 1.45 $\pm$ 0.74 mg/dL, $P = 0.028$). Small changes in SCr during hospitalization have been reported to predict long-term mortality and risk for end-stage renal disease (ESRD) requiring dialysis treatment.[7,8] Therefore, we investigated whether the observed renal benefits of nesiritide in the immediate postoperative period had any long-term impact on the incidence of mortality or requirement for dialysis.

Methods

Participants of the Nesiritide Study were included in the current analysis. The Nesiritide Study was a prospective, double blind, placebo-controlled, randomized clinical trial conducted by the nephrology and cardiovascular surgery teams at Shands Hospital at the University of Florida in Gainesville. The study was approved by the Western Institutional Review Board (WIRB), registered at the National Institutes of Health's ClinicalTrials.gov (NCT00110201)

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website, and funded by an investigator-proposed grant from Scios, Inc. Details of the Nesiritide Study as they pertain to the current analysis are presented below. Data of the participants' most recent health and renal function status were obtained using IRB-approved patient questionnaires, medical records, and the Social Security Administration's Death Master File database.

Participants of the Nesiritide Study

The eligibility criteria for participation in the Nesiritide Study have been previously reported[6] and included patients undergoing thoracic aortic aneurysm and/or cardiac valve surgery, who were older than 18 years, and who had an estimated glomerular filtration rate (eGFR, using the short version of the MDRD GFR calculator) between 30 and 90 ml/min/1.73m^2. Patients with organ transplants, preoperative intra-aortic balloon pumps, or acutely decompensated congestive heart failure were excluded from the study.

Study Protocol for the Nesiritide Study

Details of the Nesiritide Study protocol have been previously reported.[6] Eligible patients were randomized according to race, gender, and diabetes status to receive a 5-day course of continuous nesiritide (at a dose of 0.01–0.03 mcg/kg/min) or an identical-appearing placebo, starting in the operating room immediately prior to surgery. All patients received routine postoperative supportive care for their medical and surgical problems, including care for AKI, optimization of fluid and nutritional status, inotropic support, and adjustment of medication doses as appropriate for patients with renal dysfunction. The need for renal replacement therapy was determined independently by each patient's treating nephrologist per current standard of care. Postoperative GFR was calculated using the MDRD GFR calculator, and is in accordance with previous published reports.[9,10]

Outcomes

The primary endpoint of the current study was to ascertain the long-term incidence of mortality and requirement for dialysis in participants of the Nesiritide Study. AKI was defined as an absolute increase in SCr of $\geq$0.3 mg/dL from baseline within 48 hours after surgery, in accordance with the Acute Kidney Injury Network's criteria.[11]

Statistical Methods

Baseline patient characteristics are presented as mean $\pm$ standard error of the mean; comparison of variables that were evaluated as non-normally distributed was examined with the Wilcoxon rank sum test; and the *t* test was used for normally distributed values. A cumulative survival graph was plotted using Cox regression analysis. Statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

All 94 patients from the Nesiritide Study (nesiritide, n = 45; placebo, n = 49) were included in the study. Baseline patient characteristics have been previously reported[6] and include the following: mean age was 65.1 $\pm$ 12 years, 66% of the patients were male, and 92.5% were white. The mean preoperative SCr was 1.17 $\pm$ 0.29 mg/dL, the MDRD glomerular filtration rate was 63.7 $\pm$ 16.3.4 ml/min/1.73 m^2, and left ventricular ejection fraction was 49.4 $\pm$ 9.4% (n = 89). The prevalence of preexisting conditions was similar. There were no significant differences between the 2 study groups with respect to baseline demographics (age, gender, ethnicity), clinical characteristics (comorbid conditions, cardiac and renal function, Cleveland Clinic Scoring System values), type of surgery, or intraoperative parameters (duration of surgery, cardiopulmonary bypass time, aortic cross-clamp time, circulatory arrest time, incision site).[6]

Outcome Analysis

The mean follow-up period was 20.8 $\pm$ 10.4 months. Nineteen patients died during the follow-up period, 10 patients in the nesiritide group and 9 patients in the placebo group (P = 0.798). There was no difference in cumulative survival between the groups (Figure 1, nesiritide 77.7% vs placebo 81.6%, P = 0.798). Log rank tests for equality of strata did not demonstrate significant statistical differences between the placebo and nesiritide group at 3 months (P = 0.603), 6 months (P = 0.259), or 12 months (P = 0.445), using the Kaplan-Meier method. Comparison of survival rates between patients with an incidence of AKI vs no AKI demonstrated lower cumulative survival in the AKI group (Figure 2). The overall mortality rates were 41.4% in the AKI group vs 10.7% in the non-AKI group (P = 0.002). When the analysis was restricted to patients with AKI (n = 29), differences in survival time were not observed between the groups (nesiritide 16.8 $\pm$ 4 months vs placebo 18.5 $\pm$ 2.3 months, P = 0.729). In the remaining patients with no AKI (n = 65), the use of nesiritide was likewise not associated with any survival benefits (nesiritide 87.9% vs placebo 90.6%, P = 1.000).

Of the 94 patients, SCr values were available for a total of 73 patients (13 patients could not be contacted despite exhausting all available resources, and 8 patients had not undergone any laboratory testing since discharge). There were no significant differences in SCr between the groups at baseline and at hospital discharge, respectively (nesiritide vs placebo, P value): baseline 1.16 $\pm$ 0.04 vs 1.18 $\pm$ 0.04, 0.702; discharge 1.28 $\pm$ 0.08 vs 1.47 $\pm$ 0.15,

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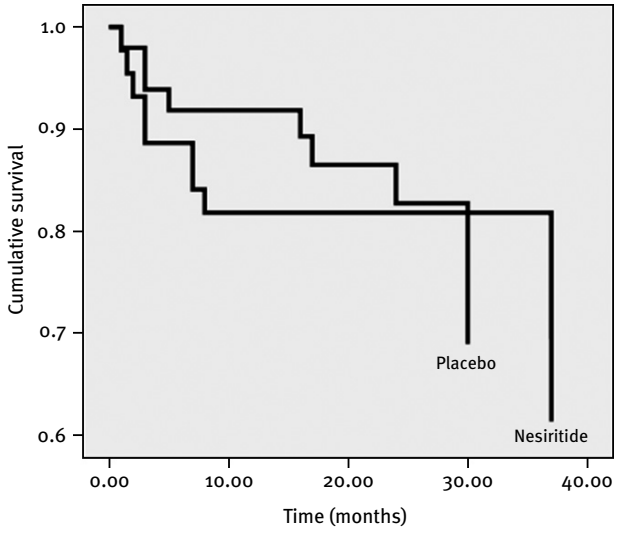

Figure 1. Long-term cumulative survival with nesiritide compared to placebo.

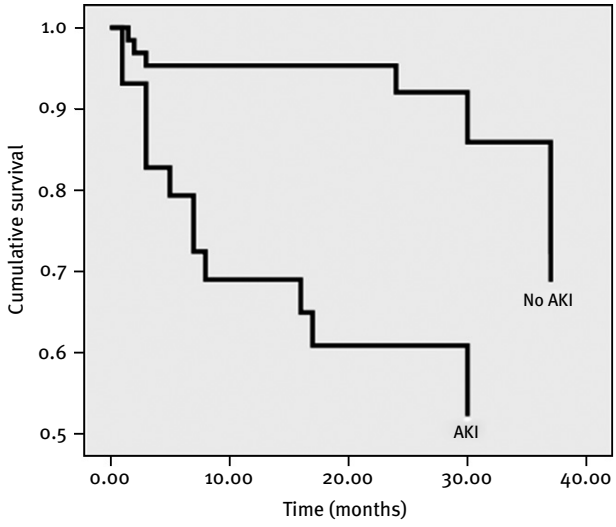

Figure 2. Cumulative survival in AKI compared to non-AKI.

0.279). However, the lack of SCr data for all patients at follow-up did not allow for estimation of progression of kidney disease status. In the Nesiritide Study, 5 patients required dialysis postoperatively. Four of the 5 subsequently died; the 1 survivor recovered renal function and no longer required dialysis. No patients required initiation of dialysis during the follow-up observation period.

Discussion

AKI following cardiovascular surgery is associated with increased mortality. Clinical interventions with natriuretic peptides and other agents that have been unsuccessful in reducing dialysis and/or all-cause mortality have generally been reported as failures.[1–4,6] However, there is interest in applying a different outcome other than dialysis and/or death in assessing efficacy in clinical trials of AKI prevention, because growing evidence suggests that in-hospital AKI not requiring dialysis may identify patients with increased long-term morbidity and mortality.[7,12] In fact, AKI has been reported to increase the risk for ESRD,[13,14] and even small changes in SCr level during hospitalization were associated with an independent higher risk of ESRD and death.[8] In CV surgery patients, deterioration of immediate postoperative renal function has been reported to predict in-hospital mortality and long-term survival.[15] In view of these observations, ascertaining the long-term effects of the observed renoprotection by nesiritide in the immediate postoperative period following CV surgery in the Nesiritide Study is of interest.

In patients with previous heart failure undergoing elective coronary artery bypass grafting, perioperative nesiritide infusion was associated with a significantly attenuated increase in SCr, a smaller reduction in eGFR, and shorter hospital stays.[9] Renoprotection was also evident in patients with moderate to severe renal dysfunction undergoing cardiopulmonary-bypass CV surgery.[16,17] These short- and intermediate-term observations are in accordance with those observed in the Nesiritide Study. However, data on long-term outcomes of the effects of nesiritide in CV surgery are not known. In this study, we were successful in collecting survival data on all patients, but we did not observe any significant difference in mortality between the groups. Figures 1 and 2 suggest a 3-phase post-operative course with an acute fall in survival in the first several months, a mid-plateau phase, and then a late-phase fall. These findings likely represent the reported 30-day and 1-, 3-, and 5-year mortality rates of 7.1%, 15%, 22.1%,[18] and 30%, respectively, for thoracic aortic aneurysm surgery,[19] and the reported 4–6%,[20] 5–8%[21] 15%,[22] and 20% mortality rates for cardiac valve surgery.[23,24] The long-term mortality rate in this study (~20%) is in accord with published data in patients undergoing CV surgery[18–26] and may be linked to the associated excess comorbidities, toxicities, and adverse pathobiological states that accelerate cardiovascular damage.[27] Consistent with data from other studies,[8,13,14] patients with AKI following cardiac surgery had reduced long-term cumulative survival compared to those with no AKI, and this was irrespective of nesiritide status. Although the nesiritide group had a lower incidence of postoperative AKI in the Nesiritide Study, this did not translate into long-term survival benefit. This observation may be explained by the relatively small sample size and event rate, but it also underscores the notion that SCr and eGFR are not validated surrogate endpoints in AKI trials. Furthermore, despite the demonstration of

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mild increase in SCr resulting in poor long-term outcomes, interventions to prevent such increases have not reduced the incidence of dialysis or the long-term mortality rates. These observations may suggest that these postoperative renoprotective effects simply reflect a transient hemodynamic effect of nesiritide unrelated to true renal protection.

Study Limitations

The estimation of progression of kidney disease could not be reliably ascertained due to the high number of patients who did not have follow-up laboratory data after discharge from the hospital (23.3%) and the data sampling interval. It has been reported that renal function improves rapidly following AKI during the first year, and then remains stable or slightly decreased over the next 10 years.[28] The small sample size also limited the ability to test the interactions of known renal risk factors on outcomes.

Conclusion

Despite these limitations, the current study suggests that the postoperative renoprotection, which we previously demonstrated with nesiritide, may not result in improved long-term survival in patients undergoing high-risk CV surgery. The long-term outcomes of interventions intended to attenuate increases in SCr are complex, and convincing demonstration of the efficacy of these interventions will require larger studies planned and powered for hard clinical endpoints including dialysis and mortality.

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