Nesiritide and clinically relevant outcomes in cardiac surgery: a meta-analysis of randomized studies

ABSTRACT

B-type natriuretic peptide is a cardiac hormone that relaxes vascular smooth muscle and causes arterial dilatation. Nesiritide has been associated with increased urine output; reduced diuretic requirements; and suppression of aldosterone, endothelin, and norepinephrine. We have independently conducted the first systematic review and meta-analysis of randomized trials to determine the impact of nesiritide on renal replacement therapy and death in patients undergoing cardiac surgery. We performed a meta-analysis of 6 randomized controlled studies including 560 patients (280 receiving nesiritide and 280 assigned to the control group). Two unblinded reviewers selected randomized trials studying nesiritide in patients undergoing cardiac surgery. Nesiritide doses ranged from 0.005 mcg/kg/min to 0.01 mcg/kg/min. Nesiritide did not reduce postoperative creatinine peak values: -0.16 [-0.42, 0.10], p for effect=0.23, p for heterogeneity<0.01, I²=90.5%) or the need for renal replacement therapy (1/177 in the nesiritide group vs 4/176 in the control group OR 0.39 [0.07, 2.06], p for effect=0.27, p for heterogeneity=0.70, I²=0%). We observed an interesting trend toward a reduction in mortality in the nesiritide group:13/280 (4.6%) vs 22/280 (7.8%) OR 0.57 [0.28, 1.15], p for effect=0.12, p for heterogeneity=0.43, I²=0%. Nesiritide did not reduce time of mechanical ventilation -8.77 hours [-21.42, 3.88], p=0.17, length of hospital stay -2.67 days [-6.50, 1.16], p=0.17 or intensive care unit (ICU) stay -0.94 days [-2.83, 0.95], p=0.33. In conclusion, further randomized controlled trials are needed to support the hypothesis that nesiritide improves clinically relevant outcomes in cardiac surgery.

Key words: Nesiritide, meta-analysis, cardiac surgery, renal replacement therapy, mortality.

Introduction

Acute renal failure is associated with significant morbidity and mortality rates. (1,2) Need for dialysis is an independent risk factor for early mortality after complicated cardiac surgery. (3,4) The pathogenesis of postoperative acute renal failure is believed to be predominantly a consequence of renal hypoperfusion and ischemia, particularly of the renal medulla. (5) Several therapeutic strategies for preserving renal function after cardiac surgery have been investigated, (6-12) but to date none have been proven effective.

Brain natriuretic peptide (BNP) is currently being investigated in the perioperative management of cardiac surgery patients and may be especially beneficial for patients with ventricular dysfunction, pulmonary hypertension, or renal dysfunction. Measured BNP levels can be used to predict postoperative complications and the risk of further cardiac events in cardiac surgery. (13-15)

Nesiritide is a recombinant B-type natriuretic peptide that is structurally identical to the endogenous hormone produced by the ventricle in response to increased wall stress, hypertrophy and volume overload. Nesiritide causes vasodilatation and may influence renal blood flow and natriuresis. It produces
Table 1. Features of included papers.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Paper</th>
<th>Surgical procedure</th>
<th>Multicentric</th>
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<td>Circ J</td>
<td>CABG</td>
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<tr>
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<td>Ann Thor Surg</td>
<td>mitral surgery</td>
<td>no</td>
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<td>Ann Pharmacotherapy</td>
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Table 2. Risk of bias assessment of included studies (Jadad Score).

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<tr>
<th>TRIAL</th>
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<th>additional/ deduct point</th>
<th>2. Was the study described as double blind?</th>
<th>additional/ deduct point</th>
<th>3. Was there a description of withdrawals and drop-outs?</th>
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<td>2</td>
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<td>-</td>
<td>0</td>
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Table 3. Preoperative creatinine values and Nesiritide Perfusion values.

<table>
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<tr>
<th>Author</th>
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<th>Preop Crea Control</th>
<th>Nesiritide Bolus (mcg/Kg)</th>
<th>Nesiritide Perfusion (mcg/kg/min)</th>
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<tr>
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<td>1,1 + 0,2</td>
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dose-related reductions in pulmonary capillary wedge pressure (preload), right atrial pressure and systemic vascular resistance and indirectly leads to increases in stroke volume and cardiac output. (16) Nesiritide is currently approved in the US for the treatment of acute decompensated heart failure. Numerous, apparently positive but inconclusive reports, targeted to surrogate end-points, have recently appeared in the literature on the use of nesiritide in subjects undergoing cardiac surgery. Nesiritide may even be associated with an increased risk of death when used for the treatment of patients with acutely decompensated heart failure. (17) To address the question whether nesiritide might influence patients' outcome after cardiac surgery, we have independently conducted an updated systematic review and meta-analysis from existing trials to determine, for the first time, the impact of nesiritide on the perioperative need for renal replacement therapy and its impact on death in patients undergoing cardiac surgery.

Materials and methods

Search Strategy Pertinent studies were independently searched in BioMedCentral, CENTRAL, and PubMed (updated June 15, 2008) by two trained investigators. The full PubMed search strategy, including the key-word, nesiritide, was developed according to Biondi-Zoccai et al. (18) and is available in the appendix. Recent (2006-2008) conference proceedings, from the International Anesthesia Research Society, American Heart Association, American College of Cardiology, American Society of Anesthesiology and European Society of Cardiology, were hand searched. In addition, we employed backward snowballing (ie scanning of references of retrieved articles and pertinent reviews) and contacted international experts for further studies. No language restriction was enforced, and non-English-language articles were translated when appropriate. References obtained from database and literature searches were first independently examined at the title/abstract level by several investigators with divergences resolved by consensus, and then, if potentially pertinent, retrieved as complete articles. The following inclusion criteria were employed for potentially relevant studies: a) random allocation to treatment, b) comparison of nesiritide versus control or other treatment, c) patients undergoing adult cardiac surgery. The exclusion criteria were: a) non-parallel design (ie cross-over) randomized trials, b) duplicate publications (in this case only the article reporting the longest follow-up was abstracted), c) non-human experimental studies, and e) no outcome data. Two investigators independently assessed compliance with selection criteria and selected studies for the final analysis, with divergences finally resolved by consensus (table 1). Baseline and outcome data were independently abstracted by several investigators with divergences resolved by consensus. Specifically, we extracted study design (including patient selection and randomization), population, clinical setting, the number of patients randomized, patients’ characteristics (preoperative creatinine), serum peak creatinine values, renal replacement therapy, adverse events, mechanical ventilation, intensive care unit (ICU) stay, length of hospital stay, death. At least two separate attempts at contacting original authors were made in case of missing data. The primary end-point of our analysis was in-hospital mortality. The co-primary endpoint was the number of patients progressing to acute kidney injury (AKI) requiring at least one episode of renal replacement therapy. Secondary end-points included peak serum creatinine levels, mechanical ventilation and the duration of ICU and hospital stay. The internal validity and risk of bias of included trials was appraised according to the Jtidad score and by completing a consensus testing. Unadjusted P values are reported throughout. Computations were performed with SPSS 11.0 (SPSS, Chicago, IL, USA), and RevMan 4.2 (a freeware available from The Cochrane Collaboration). (21) This study was performed in compliance with The Cochrane Collaboration and the Quality of Reporting of Meta-Analyses (QUOROM) guidelines.

Results

Database searches, snowballing and contacts with experts yielded a total of 9 citations. Excluding 3 non pertinent titles or abstracts, we retrieved six studies in complete form and assessed them according to the selection criteria, (22-27) which were included in the final analysis after the correspondent authors confirmed that there was no overlapping and/or duplicate publication. Five of these 6 studies were identified through database searches, while snowballing identified the sixth study. (24) Contact with experts and conference proceedings did not identify any further studies.
Study Characteristics The six randomized controlled studies included 560 patients (280 to nesiritide and 280 to the control group). All studies were performed in adult patients undergoing cardiac surgery (table 1).

All studies were of relatively high quality, with a low or moderate risk of underlying bias (table 2). One study employed a multicenter design. (22) All studies reported on mortality, while four of six studies reported data on renal replacement therapy, (23-25,27) postoperative serum creatinine peak (22,24,25,27) and ICU stay. (22,25-27) Three studies reported data on length of hospital stay (22,25,27) and mechanical ventilation. (22,25,26)

Two studies used nesiritide (24,25) infusion for 12 hours, one study for six hours (26) and other studies for at least 24 hours. (22,23,27) Nesiritide doses ranged from 0.005 mcg/kg/min to 0.05 mcg/kg/min. Brackbill et al. (27) used 2 mcg/Kg of nesiritide as bolus (table 3). Quantitative Data Synthesis Analysis showed that, in comparison to control treatment, nesiritide was not associated with clinically relevant benefits according to our major end points. Specifically, nesiritide did not reduce postoperative creatinine peak values: -0.16 [-0.42, 0.10], p for effect=0.23, p for heterogeneity<0.001, I^2=90.5% (figure1). Nesiritide also did not reduce the need for renal replacement therapy 1/177 in the nesiritide group vs 4/176 in the control group OR 0.39 [0.07, 2.06], p for effect=0.27, p for heterogeneity=0.70, I^2=0% (figure 2). There was an interesting trend toward a reduction in mortality: 13/280 (4.6%) in the nesiritide group vs 22/280 (7.8%) in the control group OR 0.57 [0.28, 1.15], p for effect=0.12, p for heterogeneity=0.43, I^2=0% (figure3). Finally, nesiritide did not reduce time of mechanical ventilation -8.77 hours [-21.42, 3.88], p for effect=0.17, p for heterogeneity=0.05, I^2=67.5%, (figure 4) length of hospital stay -2.67 days [-6.50, 1.16], p for effect=0.17, p for heterogeneity<0.001 I^2=85.6%, (figure 5) and ICU stay -0.94 days [-2.83, 0.95], p for effect=0.33, p for heterogeneity=0.10, I^2=51.5% (figure 6). Hypotension was reported by only Mentzer et al. (22) (one in the nesiritide group versus two in the control group). No significant side effect or adverse event was reported by the authors.

Discussion The most important result of this meta-analysis of six randomized controlled studies is that, in spite of promising initial reports on the beneficial effects of nesiritide, there is still no evidence of improvement in clinically relevant outcomes when using this drug. In particular, nesiritide does not reduce the need for renal replacement therapy, ICU stay, the length of hospital stay and the time of mechanical ventilation. Although no significant association between nesirit-
Natriuretic peptides are systemic and renal vasodilators that also inhibit renal tubular sodium reabsorption and renin-angiotensin-aldosterone axis activation. (28)

Nesiritide is the synthetic natriuretic peptide (recombinant BNP) which is approved for treatment of symptomatic acute decompensated heart failure. Nesiritide is a 32 amino acid peptide, similar to the naturally occurring BNP and when administered intravenously fits a two-compartment model with a rapid distribution half-life of 2 minutes. The haemodynamic effects of nesiritide, mainly consisting in the lowering of pulmonary capillary wedge pressure, and systemic vasodilatation by elevating cyclic guanosine monophosphate-coupled receptor NPR-A which is present in the endothelium. (31) During nesiritide infusions, plasma aldosterone levels decrease, combined with increased urine output and sodium excretion. (32) Nesiritide improves symptoms in patients with acutely decompensated heart failure compared with placebo and appears to be safer than dobutamine. Its short term safety, relative to standard diuretic and vasodilator therapies, is less clear. Recently, a meta-analysis of outcome data from trials on acute decompensated heart patients generated some controversy. (17) and further trials are needed to discern the effects of nesiritide therapy on renal function. Wang DJ et al. demonstrated that nesiritide infusion in decompensated heart failure patients does not improve renal function. (33)

BNP plasma levels can also be used as a marker of the presence of acute heart failure. It has been demonstrated that BNP levels rise when ventricle walls are dilated during acute heart failure. Elevated levels of BNP are not only present during primary acute heart failure but may be related to secondary right heart failure in the case of pulmonary embolism, severe lung disease or an exacerbation of established systolic dysfunction resulting from other causes. The NAPA trial was a multicenter randomized, double-blind, placebo-controlled trial of nesiritide versus placebo in 303 patients with chronic left ventricular dysfunction undergoing cardiac surgery. This study revealed that nesiritide infusion has a favorable short-term effect on renal function. Patients receiving nesiritide had greater urine output, lower peak increase in serum creatinine levels in the immediate postoperative period compared with patients receiving placebo. (22) Chen et al. demonstrated that perioperative administration of low dose nesiritide is biologically active and decreases plasma cystatin in patients with renal insufficiency undergoing cardiopulmonary bypass cardiac surgery. (23)

In studies in which patients received standard congestive heart failure therapy (diuretics, dopamine), nesiritide therapy lowered pulmonary capillary occlusion pressure and resolve dyspnea more rapidly than nitroglycerin and placebo. (30) Nesiritide showed a dose-dependent arterial and venous vasodilatation effect, mediated by the activation of cyclic guanosine 3-5 monophosphate-coupled receptor NPR-A which is present in the endothelium. (31) During nesiritide infusions, plasma aldosterone levels decrease, combined with increased urine output and sodium excretion. (32) Nesiritide improves symptoms in patients with acutely decompensated heart failure compared with placebo and appears to be safer than dobutamine. Its short term safety, relative to standard diuretic and vasodilator therapies, is less clear. Recently, a meta-analysis of outcome data from trials on acute decompensated heart patients generated some controversy. (17) and further trials are needed to discern the effects of nesiritide therapy on renal function. Wang DJ et al. demonstrated that nesiritide infusion in decompensated heart failure patients does not improve renal function. (33)

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Limitations. We analyzed data from six
studies which have different inclusion criteria. Therefore, patients included might have differed significantly in baseline clinical characteristics. Different clinical conditions (such as renal dysfunction, heart failure, valvular defects), therapeutic protocols, and surgical scenarios may affect the effectiveness of nesiritide.

Conclusions. Our meta-analysis demonstrated that nesiritide is not yet an established method for the prevention of acute renal failure and mortality in cardiac surgery. Further randomized controlled studies are warranted.

APPENDIX

PubMed search strategy according to Biondi-Zoccai et al. (18)


REFERENCES