Lack of renoprotective effect of i.v. N-acetylcysteine in patients with chronic renal failure undergoing cardiac surgery

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Background. Pre-existing chronic renal failure is a significant risk factor for acute renal failure (ARF) after cardiac surgery. N-acetylcysteine (NAC) has been shown to prevent contrast media-induced ARF. Our objective was to evaluate whether i.v. NAC has renoprotective effects in patients with mild renal failure undergoing cardiac surgery.

Methods. In this prospective, randomized, double-blind study, 80 patients with mild to moderate renal failure undergoing elective heart surgery with cardiopulmonary bypass were recruited. All received either i.v. NAC (n=38) or placebo (n=39) at induction of anaesthesia and then up to 20 h. Urine N-acetyl-β-D-glucosaminidase (NAG) and urine creatinine ratio, plasma creatinine, and serum cystatin C levels indicated renal function.

Results. Levels of urinary NAG/creatinine ratio, plasma creatinine and serum cystatin C did not significantly differ between NAC and placebo groups during five postoperative days. Urine NAG/creatinine ratio increased over 30% in 100% of patients in the NAC group vs 92.3% in the placebo group (P=0.081). Plasma creatinine increased by 25% from baseline or over 44 μmol litre⁻¹ in 42.1% in NAC group vs 48.7% in placebo group (P=0.560). Serum cystatin C exceeded 1.4 mg litre⁻¹ in 78.9% in NAC group vs 61.5% in placebo group (P=0.096).

Conclusions. Prophylactic treatment with i.v. N-acetylcysteine had no renoprotective effect in patients with pre-existing renal failure undergoing cardiac surgery.

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Renal failure is a serious complication after cardiac surgery, resulting in increased mortality and morbidity, and a longer stay in intensive care, particularly if haemodialysis is required.1 Acute renal dysfunction occurs in 7.7% of patients after cardiac surgery, with 0.7–1.4% requiring transient renal replacement therapy.1,2 The cause of renal impairment is multifactorial; increased age, elevated preoperative serum creatinine, diabetes mellitus, reduced cardiac ejection fraction and the duration of cardiopulmonary bypass (CPB) can independently increase the risk of acute renal failure (ARF) or dysfunction.1,2 Circulatory failure during cardiac surgery can cause ischaemia and toxic injury to the kidneys, which leads both to depletion of local antioxidants and to the formation of free oxygen radicals.3

N-acetylcysteine (NAC) has antioxidant properties and acts as a vasodilatator. It elevates levels of cyclic guanosine monophosphate and stimulates the release of nitric oxide-derived relaxing factor.4 Studies performed on patients with renal failure have provided promising results with NAC in prevention of the worsening of renal damage induced with contrast media.5-6 The effects of NAC on renal protection during cardiac and aortic surgery have been studied recently with both negative7,8 and positive9 results. The inconsistency in the findings of these studies may, however, be attributable to the fact that these studies have not consisted of patients with preoperative renal failure.

The aim of this double-blind, randomized and placebo-controlled study was to evaluate whether i.v. NAC has renoprotective effects in patients with pre-existing chronic renal failure undergoing cardiac surgery. The merits of NAC in ARF have been associated with amelioration of oxidative stress-induced tubular injury.3 To detect the effect
of NAC on tubular function, we measured urine levels of N-acetyl-β-D-glucosaminidase (NAG), together with the levels of serum cystatin C and plasma creatinine.

**Methods**

After approval by the Ethics Committee of the Surgical Clinic of the Helsinki University Hospital and by the Finnish National Agency for Medicines, written informed consent was obtained from 80 patients. Eligible patients had preoperative plasma creatinine values above the upper range limit (>100 μmol litre⁻¹) in our laboratory, and were scheduled for open-heart surgery with CPB. Exclusion criteria were plasma creatinine level above 400 μmol litre⁻¹, chronic renal replacement therapy, kidney transplantation, and known or suspected allergy to NAC. None of the patients had received radio contrast therapy or NAC within 1 month before surgery. Non-steroidal anti-inflammatory drugs were discontinued 1 day, and acetylsalicylic acid 5 days before surgery.

Before induction of anaesthesia, half of the 80 patients were randomly allocated to receive N-acetylcysteine (Group NAC), and the other half placebo (Group Placebo) in a double-blind manner. NAC (Parvolex®, Celltech Pharmaceuticals Ltd, Slough, UK) was administered in saline 0.9% as a loading dose of 150 mg kg⁻¹ in 15 min, followed by 50 mg kg⁻¹ for the next 4 h, and thereafter, 100 mg kg⁻¹ for 16 h. The placebo group received similar volumes of saline 0.9%. The Hospital pharmacy performed the randomization and prepared study medications.

Patients received their routine cardiac medication until the morning of surgery, except for angiotensin-converting enzyme inhibitors and angiotensin II-receptor antagonists. They were premedicated with oral lorazepam (0.06 mg kg⁻¹) and anaesthetized with etomidate (0.2 mg kg⁻¹), sufentanil (2 μg kg⁻¹) and rocuronium (0.6 mg kg⁻¹). Anaesthesia was maintained with continuous infusions of sufentanil (1–2 μg kg⁻¹ h⁻¹) and propofol (4–8 mg kg⁻¹ h⁻¹), supplemented with inhaled isoflurane in order to keep the bispectral index below 50. Neuromuscular block was achieved when needed with incremental doses of rocuronium. None of the patients received aprotinin.

The CPB circuit consisted of a roller pump, a non-heparin-coated circuit, a membrane oxygenator, an arterial filter and an open venous reservoir system. The CPB circuit was primed with 2000 ml acetated Ringer’s solution (RAC) and mannitol 6% (100 ml). Additional mannitol 6% (100 ml) was given before the opening of the aortic cross-clamp. RAC was added as required to guarantee the filling volume of the circuit. During CPB, hypothermia (32–34°C) was induced, and flow rate was maintained at a level of 2.4 litre min⁻¹ m⁻². Perfusion pressure was maintained between 60 and 90 mm Hg by intermittent boluses of norepinephrine. Myocardial protection consisted of crystalloid cardioplegia with blood in a ratio of 4:1 or 8:1. Before termination of CPB, the patients were rewarmed to 36°C. After weaning from CPB the entire content of the circuit was collected and returned to the patient. Propofol was used for sedation in the intensive care unit (ICU), where the patients were weaned from the respirator according to the hospital’s routine guidelines.

All patients were continuously monitored using ECG, and radial artery cannula for arterial pressure recording and blood sampling. After induction of anaesthesia, a pulmonary artery catheter was introduced through the right internal jugular vein for monitoring of haemodynamic variables and for continuous measurement of mixed venous haemoglobin saturation (Svo₂). Haemodynamic variables were systolic arterial pressure, heart rate (HR), central venous pressure, pulmonary artery pressure, cardiac index and pulmonary capillary wedge pressure (PCWP). Each was recorded before administration of the study medication, after CPB, at the end of surgery, at admission to the ICU and at 6, 12 and 18 h after admission. In addition, mean arterial pressure (MAP) and HR were recorded every 5 min with routine computerized data collection. The urinary bladder catheter and probes for the measurement of nasopharyngeal and bladder temperature were also inserted after induction of anaesthesia.

During induction, each patient received a 500 ml bolus of RAC, followed by continuous infusion of RAC 80 ml h⁻¹ for the first 24 h. During CPB, additional RAC was added to the CPB circuit to keep volume above the minimal level of the venous reservoir.

After CPB and in the ICU additional fluid (RAC or albumin 4%) was administered according to routine postoperative care, maintaining PCWP between 10 and 14 mm Hg. Red blood cells were transfused when haemoglobin concentration fell below 60 g litre⁻¹ during extracorporeal circulation or below 85 g litre⁻¹ after operation.

Norepinephrine (0.01–0.1 μg kg⁻¹ min⁻¹) was started whenever mean systemic arterial blood pressure fell below 70 mm Hg despite adequate filling pressures. Epinephrine infusion (0.02–0.2 μg kg⁻¹ min⁻¹) was initiated when the cardiac index remained under 2.5 litre min⁻¹ m⁻² or Svo₂ under 65%. Milrinone and an intra-aortic balloon pump (IABP) were available for further cardiac support.

Urinary output was recorded from the insertion of the urinary catheter until 24 h after start of the trial medication. If urinary output remained under 0.5 ml kg⁻¹ h⁻¹ after CPB, furosemide was given as incremental boluses of 10–20 mg or as an infusion of 0.01–0.04 mg kg⁻¹ h⁻¹ i.v. The doses of furosemide were recorded.

Urinary samples for analysis of U-NAG and urinary creatinine were handled as follows: baseline values came from a morning urine specimen given before surgery, the next samples were from urine excreted from the insertion of the urinary catheter to the start of CPB, from the initiation of CPB until the end of surgery, during 0–6 h after operation, 6–12 h after operation and finally on the fifth
N-acetylcysteine and cardiac surgery

day after operation. To minimize the effect of variation in urine concentration, the urine NAG/creatinine ratio was calculated.

Blood samples for plasma creatinine and serum cystatin C were obtained before the trial medication, and in the morning of the first, third and fifth day after surgery.

Plasma and urine samples were stored at −20°C and analysed at the Helsinki University Central Hospital Laboratory. Serum cystatin C concentrations were analysed with the DAK Cytomation Denmark A/S (Glostrup, Denmark) particle-enhanced immunoturbidimetric cystatin C assay adapted for the Hitachi 917 analyser (Tokyo, Japan). The within-series coefficient of variation (CV) was 2.0% at 0.71 mg litre⁻¹, and the between-series CV was 4.2, 2.9 and 5.7% at 0.66, 1.25 and 5.08 mg litre⁻¹, respectively. NAG was measured by a colorimetric assay (Roche Diagnostics GmbH, Mannheim, Germany) adapted for the Hitachi 917 analyser and calibrated with the Roche NAG standard (Cat. No 982962) from beef kidney. The within-series CV was 2.1 and 3.0% at 8.9 and 4.7 unit litre⁻¹, respectively, and the between-series CV was 5.2% at 8.0 unit litre⁻¹. Plasma and urine creatine were analysed with the enzymatic CREA-plus assay method of Roche Diagnostics GmbH on a Hitachi Modular analyser. The urinary NAG/creatinine ratio was calculated by dividing the value of NAG (unit litre⁻¹) with that of creatinine (µmol litre⁻¹).

The outcome measure was an increase in the urine NAG/creatinine ratio at 30% above baseline. Changes in plasma creatinine and serum cystatin C were also measured. ARF was also defined using the following criteria: finding the serum cystatin C level over 1.4 mg litre⁻¹ and increase of plasma creatine over 25% from the baseline or an increase of more than 44 µmol litre⁻¹. In addition, we recorded 30 day mortality, renal replacement therapy, length of ICU stay and possible side-effects.

Statistics

Based on earlier data, the sample size was calculated as 40 patients per group for the trial to have 80% power in detecting a significant (30%) difference in the levels of NAG at 95% CI limits (α = 0.05). Comparisons between groups were performed with repeated measures ANOVA and the independent samples t-test. The χ²-test served for categorical variables, followed by Fisher’s exact test when appropriate. A P-value <0.05 was considered statistically significant. All analyses were by intention-to-treat (ITT). Results are expressed as mean (SD) unless otherwise indicated. Statistical analyses were performed with statistical software (SPSS package, version 11.5, Chicago, IL, USA).

Results

Two patients of the NAC group were excluded from further analysis; one as a result of a protocol violation in which the attending nurse accidentally stopped the drug infusion after 12 h and the other because the operation was switched to off-pump coronary artery bypass (OPCAB). One patient of the placebo group underwent OPCAB. For baseline characteristics and intraoperative data see Table 1. The baseline renal function was similar between the two groups as measured by preoperative plasma creatinine level (Fig. 1A).

We found no differences between the groups in plasma creatinine or serum cystatin C (Fig. 1A and B). No differences existed between the groups in the urine NAG/creatinine ratio (Fig. 2).

Comorbidities

Diabetes, n (%) 13 (34.2) 15 (38.5) 0.698
Hypertension, n (%) 17 (44.7) 19 (48.7) 0.726
Peripheral vascular disease, n (%) 6 (15.8) 9 (23.1) 0.420

Table 1 Baseline characteristics. NYHA, congestive heart failure classes 3–4; LVEF, ejection fraction of the left ventricle; GFR, glomerular filtration rate; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve reconstruction; CPB, cardiopulmonary bypass. Values are mean (range) or mean (SD) or number of patients (%). P-values calculated by χ²-test and independent samples t-test

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N-acetylcysteine group (n=38)</th>
<th>Placebo group (n=39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG, n (%)</td>
<td>34 (89.5)</td>
<td>29 (74.3)</td>
<td>0.086</td>
</tr>
<tr>
<td>AVR, n (%)</td>
<td>14 (36.8)</td>
<td>11 (28.2)</td>
<td>0.418</td>
</tr>
<tr>
<td>MVR, n (%)</td>
<td>4 (10.5)</td>
<td>10 (25.6)</td>
<td>0.086</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>119 (5)</td>
<td>129 (8)</td>
<td>0.097</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>81 (4)</td>
<td>88 (7)</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Discussion

This randomized double-blind study demonstrates that in patients with pre-existing mild to moderate chronic renal
failure undergoing cardiac surgery, i.v. NAC has no renoprotective effects. Postoperative increases in plasma creatinine, serum cystatin C and urine NAG/creatinine ratio after i.v. NAC did not significantly differ from those recorded after placebo.

The present study agrees with our recent study in which NAC was equal to placebo in renal protection during abdominal aortic reconstruction. Our results are also in line with those reported in the study by Burns and colleagues, which was published before our study was completed. However, another recent retrospective study suggested that NAC would protect the kidneys during cardiac surgery. Such a large dose was chosen in our study because similar doses have been effective in organ protection in a number of studies performed in hepatic failure. The antioxidant and anti-inflammatory effects of NAC are also dose related and fully demonstrable only after high doses.

The growing body of evidence supports the pivotal role of inflammatory mechanisms in the pathogenesis of ARF after cardiac surgery. Neutrophil activation and release of reactive oxygen-derived substances contribute to post-cardiac surgery renal injury and increased levels of both tumour necrosis factor alpha (TNF-α) and interleukin-8 (IL-8) are associated with proximal tubular injury. NAC may provide renal protection by acting as an antioxidant and arteriolar vasodilator via the nitrous oxide pathway. In experimental studies NAC has prohibited renal deterioration by producing a variety of anti-inflammatory and antioxidant effects such as antagonism of TNF-α and inhibition of the expression of the vascular cell adhesion molecule.

In the clinical setting NAC has prevented pump-induced oxidoinflammatory responses during CPB and oxidative stress-induced proximal tubular injury during angiography. Although we were not able to measure plasma levels of cytokines or reactive oxygen-derived species, our results suggest mechanisms other than those inhibited by
within the kidney, proximal tubular epithelial cells are the most vulnerable to injury, ranging from dysfunction to severe damage. Various markers of renal tubular damage (α1-microglobulin, glutathione transferase-α and π. NAG) increase after cardiac surgery and there is a correlation especially between urinary levels of NAG and tubular injury. In the present study urine NAG/creatinine levels increased significantly from baseline, yet without any effect of NAC.

Although it has been demonstrated that tubular enzymuria might serve in early detection of renal impairment in the ICU, tubular injury during cardiac surgery is not necessarily associated with renal dysfunction after surgery. So far, no evidence has appeared that perioperative increase of these markers leads to postoperative morbidity or mortality. Furthermore, no consensus exists as to the definition of ARF after surgery.

In the study assessing the effects of NAC on contrast nephropathy, Gill and colleagues suggested that adequate hydration alone would be as effective as NAC in renal protection. We used a strict protocol for volume replacement therapy according to the preset cardiac filling pressures, resulting in an extremely positive fluid balance during the first postoperative day. This controlled hydration would have uncovered a renoprotective effect of NAC, if any. The fluid balance was more positive for patients receiving NAC than for those receiving the placebo, which suggests a vaso-dilatory effect of NAC. Patients who received NAC bled somewhat more than did those who received the placebo, which might be because of the anticoagulant effects of NAC.

Our study was statistically powered to detect any possible benefits of NAC for tubular function. Although the increase of U-NAG can explain the possible tubular damage, it cannot be considered a clinically significant marker of kidney failure. More patients would have been required to assess the ARF using clinically more practical indicators such as the increase in the creatinine or the need for renal replacement therapy. Including patients undergoing three different operations: coronary bypass, valve and
valve with bypass surgery is another limitation of our study. On the other hand, we detected renal deterioration with multiple indicators.

In conclusion, ARF associated with cardiac surgery in patients with chronic mild to moderate renal failure could not be prevented by prophylactic administration of a large dose of i.v. NAC. Even when measured with various and sensitive markers, no difference in renal function appeared between patients who received NAC or placebo.

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