Efficacy of N-acetylcysteine in preventing renal injury after heart surgery: a systematic review of randomized trials

Adabag AS, Ishani A, Bloomfield HE, Ngo AK, Wilt TJ

CRD summary
This review concluded that, in patients undergoing cardiac surgery, prophylactic perioperative N-acetylcysteine did not reduce the risk of acute renal injury, haemodialysis or death. However, the findings of the review should be interpreted with some degree of caution given the risk of missing data and the limitations of the included data and analyses.

Authors’ objectives
To assess the efficacy and safety of perioperative N-acetylcysteine for the prevention of renal injury in adults undergoing cardiac surgery.

Searching
MEDLINE was searched for studies published in English from 1960 to January 2008. Search terms were reported. Additional studies were identified through searching the ClinicalTrials.gov website, checking reference lists of relevant publications and contacting authors of identified studies.

Study selection
Randomised controlled trials (RCTs) in adults, where at least one treatment group received either oral or intravenous N-acetylcysteine, immediately before, during or after cardiac surgery, were eligible for inclusion in the review. The inclusion of intervention regimens were not limited by dose or duration. Eligible trials had to report baseline and postoperative (within five days of surgery) creatinine levels or incidence of acute renal injury. Secondary outcomes included maximum change in serum creatinine from baseline (within five days of surgery), postoperative haemodialysis, all-cause mortality and duration of stay in intensive care unit or in hospital.

Included trials were published between 2005 and 2008, and carried out in Canada, USA, Australia, Finland, Germany, Italy and Turkey. Regimens of N-acetylcysteine varied in dose, duration and route of administration, but the majority assessed intravenous N-acetylcysteine. All but one of the trials compared N-acetylcysteine with placebo; the remaining trial compared N-acetylcysteine with usual care. Just over half of the trials included high-risk patients. High-risk patients were judged on the basis of factors including baseline chronic kidney disease, age (70 years or over), diabetes mellitus, left ventricular ejection fraction (below 35%), New York Heart Association functional class (III/IV), and valve, re-do or urgent surgery. Seventy-one percent of included patients were male and the mean age of participants was 70 years. In total, 66% of patients underwent coronary artery bypass graft surgery alone or combined with valve surgery. Patients commonly had co-morbid conditions including diabetes mellitus, heart failure, and prior myocardial infarction. The mean duration of follow-up for creatinine levels was 8.2 days (range three to 30 days) post-surgery.

Two reviewers assessed the each study for inclusion and discrepancies were resolved through discussion.

Assessment of study quality
Methodological quality was judged according to: concealment of treatment allocation; similarity of trial groups at baseline; blinding of the patient, clinician and outcome assessor; point estimates and measures of variability for the primary outcome variable; and application of intention-to-treat analysis.

The authors did not state how many reviewers performed the assessment.

Data extraction
Where possible, risk ratios (RRs) with 95% confidence intervals (CIs) were reported for dichotomous outcomes, and means with standard deviations for continuous outcomes. Trial authors were contacted for further information and data where necessary.
Two reviewers extracted the study data and disagreements were resolved through discussion.

**Methods of synthesis**
Trials were grouped by outcome and effect sizes pooled using a random-effects model where judged clinically appropriate and statistically feasible. Weighted mean differences (WMD) were calculated for continuous outcomes and weighted risk ratios for dichotomous outcomes; both with 95% confidence intervals. Statistical heterogeneity was assessed using the I² statistic. Pre-specified subgroup analyses were performed according to the risk profile of patients and the route of administration of N-acetylcysteine.

**Results of the review**
Ten RCTs (n=1,163 patients) were included in the review; sample sizes ranged from 20 to 295 patients. Allocation concealment was judged as adequate in all but two trials, where concealment was unclear. Five trials used intention-to-treat analysis (four unclear and one not used). Drop-outs were reported in half of the trials. Only three trials reported adverse events.

There were no statistically significant differences between N-acetylcysteine and control groups for acute renal injury incidence (nine RCTs), haemodialysis (10 RCTs), mortality (10 RCTs), duration of intensive care unit (eight RCTs) or hospital (six RCTs) stay, or maximum change in serum creatinine from baseline (eight RCTs). There was no evidence of significant heterogeneity (I²=0%) for acute renal injury, haemodialysis and mortality; moderate to high levels of heterogeneity were reported for maximum change in creatinine (I²=50%), intensive care unit length of stay (I²=94%) and total length of hospital stay (I²=55%). The authors reported a trend towards reduced acute renal injury incidence among patients with baseline chronic kidney disease favouring intravenous N-acetylcysteine (two RCTs), but this was also not statistically significant.

Subgroup analyses showed that patient risk profile and route of N-acetylcysteine administration were not significantly associated with acute renal injury.

**Authors’ conclusions**
In patients undergoing cardiac surgery, prophylactic perioperative N-acetylcysteine did not reduce the risk of acute renal injury, haemodialysis or death.

**CRD commentary**
This review answered a clearly defined research question. Searches were carried out for both published and unpublished studies, although only studies published in English appeared to have been eligible for inclusion, so relevant data may have been missed. Some attempts were made to reduce the risk of reviewer error and bias when selecting studies and extracting their data; but it was unclear whether similar precautions were taken when assessing the quality of the data.

The quality of the trials was assessed using relevant criteria, although the findings were not reported for all assessment criteria (e.g. blinding). The quality of the trials varied, as did their clinical characteristics, particularly with respect to intervention regimens and participant characteristics. Trials were pooled using appropriate methods and statistical heterogeneity appeared to be low or absent. Some attempts were made to examine the potential effects of a limited number of potential clinical variables within the trials. The authors also discussed a number of limitations relating to the choice of surrogate outcome measures, and the size and duration of the trials, which may have affected the reliability of the findings.

The findings of the review should be interpreted with some degree of caution given the risk of missing data and the limitations of the included data and analyses.

**Implications of the review for practice and research**
**Practice:** The authors stated that the use of N-acetylcysteine in patients undergoing cardiac surgery is not supported by evidence.
Research: The authors stated that further RCTs are required to determine whether intravenous N-acetylcysteine improves acute renal injury, haemodialysis, death or length of stay in hospital/intensive care unit, in patients with baseline chronic kidney disease. The authors also stated that it may be prudent to make baseline chronic kidney disease a compulsory inclusion criterion in future studies.

Funding
Department of Veterans Affairs Health Services Research and Development Program, USA; Minneapolis/VISN-23 Center for Chronic Diseases Outcomes Research (CCDOR), USA; Veterans Administration Clinical Science Research and Development Service, grant number 04S-CRCOE 001; National Institute of Diabetes and Digestive and Kidney Diseases (NODDK) RO1, grant number DK063300-01A2.

Bibliographic details

PubMedID
19282300

DOI
10.1093/eurheartj/ehp053

Original Paper URL
http://eurheartj.oxfordjournals.org/content/30/15/1910.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetylcysteine /therapeutic use; Acute Kidney Injury /prevention & control; Aged; Antioxidants /therapeutic use; Female; Humans; Male; Perioperative Care; Randomized Controlled Trials as Topic; Risk Factors; Thoracic Surgical Procedures /adverse effects; Treatment Outcome

AccessionNumber
12009108467

Date bibliographic record published
10/03/2010

Date abstract record published
30/06/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.