Meta-analysis of N-acetylcysteine to prevent acute renal failure after major surgery

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CRD summary
The authors found that peri-operative N-acetylcysteine did not reduce mortality or acute renal failure after major surgery in adults when radio contrast was not used. The review was well conducted and the conclusions appear reliable.

Authors' objectives
To assess the effects of N-acetylcysteine on mortality and renal outcomes among patients who underwent major surgery without radio-contrast.

Searching
Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE were searched. Search dates varied across sources and spanned 1966 to February 2008. Search terms were reported. The reference lists of retrieved studies and related articles were handsearched, as were the websites of the International Network of Agencies of Health Technology Assessment and the International Society of Technology Assessment in Healthcare. The search was not restricted by language.

Study selection
Randomised controlled trials (RCTs) in perioperative settings that compared N-acetylcysteine with placebo for adults who underwent major surgery were eligible for inclusion, provided radio contrast was not used. The primary outcomes for the review were mortality and acute renal failure that required dialysis. Other outcomes of interest included rates of increase in serum creatinine more than 25% above baseline (or more than 0.50mg per dL), surgical re-exploration for bleeding, length of intensive care unit stay and amount of allogeneic blood transfusion required. Studies of N-acetylcysteine for patients with sepsis, acute respiratory distress syndrome or radio contrast nephropathy were excluded, as were studies in which N-acetylcysteine was administered as part of a multi-oxidant supplement.

Participants in studies in the review underwent elective cardiac surgery, abdominal aneurysm repair or abdominal cancer surgery. Most had normal renal function preoperatively, although some of the cardiac surgery studies were restricted to participants with pre-existing renal impairment. N-acetylcysteine was in most cases given intravenously through the whole peri-operative period at a mean dose of about 15,300 mg (range 2,400 to 35,000 mg per 75kg patient); some studies used an oral dose pre-operatively. Controls in most cases received an equivalent volume of intravenous 5% dextrose or 0.9% saline.

Two reviewers checked the eligibility of selected trials, but the authors stated neither how the papers were initially selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed randomisation method, allocation concealment, blinding, use of intention to treat analysis and inclusion/exclusion criteria. There were no disagreements between the reviewers.

Data extraction
Odds ratios with 95% confidence intervals (CIs) were calculated for dichotomous outcomes and mean differences for continuous outcomes. If necessary (such as for data on length of intensive care unit stay), means and standard deviations were estimated from medians and interquartile ranges reported in the studies. Two reviewers independently extracted the data using a pre-designed form. There were no disagreements.

Methods of synthesis
Studies were grouped according to outcome and pooled odds ratios or weighted mean differences with 95% CIs calculated using a random-effects analysis. Statistical heterogeneity was assessed using the $\chi^2$ test and the $I^2$ statistic. Subgroup analyses were conducted to examine effects in studies of cardiac surgery, pre-existing renal impairment and
higher doses of N-acetylcysteine.

**Results of the review**

Ten RCTs were included (n=1,193, range 40 to 295). Overall study quality was good: all RCTs were double blinded; nine had adequate allocation concealment; and seven used intention to treat analysis.

There was no statistically significant difference between the N-acetylcysteine group and the placebo group in rates of mortality (odds ratio 1.05, 95% CI: 0.58 to 1.92; 10 RCTs), acute renal failure requiring dialysis (odds ratio 1.04, 95% CI: 0.45 to 2.37; seven RCTs) or incremental increase in serum creatinine concentration more than 25% above baseline (odds ratio 0.84, 95% CI: 0.64 to 1.11; six RCTs); length of intensive care unit stay (weighted mean difference 0.46 days, 95% CI: -0.43 to 1.36; seven RCTs); risk of surgical re-exploration (odds ratio 1.16, 95% CI: 0.57 to 2.38; six RCTs); or amount of allogeneic blood transfusion required (weighted mean difference 0.31 units, 95% CI: -0.21 to 0.84). There was significant heterogeneity for the outcome of length of intensive care unit stay ($I^2=86.1\%$), but not for the other outcomes.

Subgroup and sensitivity analyses did not change the statistical significance of any findings; sample numbers for some subgroups were small.

**Authors' conclusions**

Peri-operative N-acetylcysteine did not reduce mortality or acute renal failure after major surgery when radio contrast was not used.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies without language restriction. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently make decisions on data and extraction and validity assessment, but it was unclear how the initial selection of potentially eligible studies was conducted. Appropriate statistical methods were used to combine the data, assess for heterogeneity and explore differences between the studies. Other potential sources of bias (such as small sample size) were addressed in the text. The review was well conducted and the authors' conclusions appear reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that it would be reasonable to administer N-acetylcysteine prophylaxis to prevent radio contrast nephropathy in patients at high risk of bleeding, based on extrapolation of the safety data from this review to other patient groups.

**Research:** The authors stated that a large RCT was needed to confirm whether peri-operative N-acetylcysteine was beneficial in patients with pre-existing renal impairment.

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