Meta-analysis of randomized clinical trials on the usefulness of acetylcysteine for prevention of contrast nephropathy

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CRD summary
The meta-analysis assessed the usefulness of N-acetylcysteine (NAC) for the prevention of contrast nephropathy. The authors concluded that routine prophylactic NAC use in patients with stable chronic renal insufficiency or diabetes who are undergoing elective angiography can be recommended. Given the limitations in the selection of studies and varying results among them, the conclusions should be regarded with caution.

Authors' objectives
To evaluate the usefulness of N-acetylcysteine (NAC) for the prevention of contrast nephropathy.

Searching
PubMed, EMBASE, BIOSIS Previews, online clinical trial databases, conference abstracts, and the bibliographies of relevant articles were searched. The search terms were reported but not the search period. Related articles were tracked. Only studies published in English in peer-reviewed journals were eligible for inclusion in the review.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies of NAC and saline hydration compared with saline hydration alone, with or without placebo arm, given before angiography or computed tomography (CT) were eligible for inclusion. Most of the included studies administered 600 mg NAC twice a day, starting one day before the contrast intake; other studies used doses that varied between 400 and 1,200 mg, and some studies started the medication on the day of the intervention only. All of the included studies used nonionic, low-osmolar contrast, and the mean contrast volume ranged from 75 to 197 mL. In most studies the hydration regimen was a normal saline 1 mL/kg per hour starting 12 hours before contrast.

Participants included in the review
The review did not specify any inclusion criteria for the participants. The participants in the included studies had baseline renal insufficiency with mean creatinine levels ranging from 1.4 to 2.8 mg/dL, and were scheduled for coronary angiography with or without angioplasty or CT. The proportion of patients with diabetes mellitus ranged from 33 to 64% across the included studies.

Outcomes assessed in the review
The studies had to measure serum creatinine 48 hours after contrast agent intake to be eligible for inclusion. The review also assessed the incidence of contrast nephropathy, the mean creatinine change from baseline to the 48-hour measurement (continuous data), and the need for dialysis. Contrast nephropathy was defined as an increase in serum creatinine of more than 0.5 mg/dL, or as more than 25% of the baseline creatinine level.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Three reviewers independently assessed studies for use and appropriateness of randomisation and blinding, description of withdrawals and drop-outs, methods used for statistical analysis, reporting of inclusion and exclusion criteria, and
methods used to record adverse effects. The quality scores ranged from 0 to a maximum of 8. Any discrepancies were resolved through consensus.

Data extraction
Three reviewers independently extracted the data. The reviewers extracted patient characteristics, baseline and 48-hour creatinine levels, mean creatinine change, dichotomised prevalence data for contrast nephropathy and dialysis need, relative risk, relative risk reduction, absolute risk difference, P-values and 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
The studies were combined using the random-effects model of DerSimonian and Laird. Pooled odds ratios (ORs), risk differences, mean creatinine change at 48 hours and the number-needed-to-treat (NNT) were calculated. The issue of publication bias was examined using the methods described by Begg and Mazumdar, Egger et al, and Rosenthal's file-drawer method.

How were differences between studies investigated?
Clinical differences between the studies were assessed and evaluated as similar enough to allow statistical pooling. Statistical heterogeneity was assessed but the method was not stated. Sensitivity analyses assessed the relative influence of each study through excluding each study in turn. Meta-regression analyses were used to assess the effects of baseline serum creatinine, proportion of diabetics, age, contrast volume and sample size.

Results of the review
Seven RCTs (n=805) met the inclusion criteria.

Overall, the quality of the studies was considered fair with a mean score of 4 out of 8 (range: 1 to 8). Methodological flaws included inappropriate descriptions of the following: randomisation (3 studies), blinding (3 studies), withdrawals (3 studies), inclusion and/or exclusion criteria (2 studies) and monitoring of adverse effects (6 studies).

The odds of developing contrast nephropathy were significantly lower for patients administered NAC than for those given placebo (OR 0.37, 95% CI: 0.16, 0.84; based on 7 studies). The pooled risk difference was -0.11 (95% CI: -0.19, -0.03), which corresponded to an NNT of 9 (95% CI: 5, 33). There was evidence of statistical heterogeneity (P=0.012).

There was no evidence of publication bias; to negate the statistical significance of the calculated effect size, 339 studies showing no effect (with comparable sample size and P=0.06) would be required.

Dialysis was required in three patients in each treatment (OR 0.95, 95% CI: 0.31, 2.90).

The weighted mean change in creatinine was -0.22 mg/dL (95% CI: -0.35, -0.09).

The meta-regression analysis did not identify any significant effects on the pooled outcome.

Cost information
The review reported that the administration of NAC has a low cost (less than $3.00 per 4-dose regimen at U.S. federal government rates).

Authors' conclusions
It is reasonable to recommend routine prophylactic NAC use in patients with stable chronic renal insufficiency or diabetes who are undergoing elective angiography.

CRD commentary
The review stated a clear question and inclusion criteria. The search was relatively thorough, but only studies published in English language peer-reviewed journals were eligible for inclusion. Identified unpublished studies were excluded. This procedure can introduce language and publication bias, suggesting that the treatment effect may be overrated. The review assessed the potential for publication bias. The reviewers undertook measures to reduce errors and bias in the data extraction and validity assessment, but not in the selection of studies. The validity of the included studies was assessed and results were reported.

There was little information on the participants in the included studies, although judging from the discussion in the review only a selected patient population (at increased risk at baseline) was studied. The number of studied patients was small. The pooled analysis showed evidence of statistical heterogeneity and the source was not identified, leaving some doubt about the clinical usefulness of the pooled result. The review assessed NAC in conjunction with saline hydration but the conclusions did not make this clear. Given the potential bias in the selection of studies and unexplained heterogeneity of pooled results, the conclusions should be regarded with caution. (See Other Publication of Related Interest for a review of published and unpublished studies on the same topic, which may be of interest.)

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

Practice: The authors stated that prophylactic NAC should be routinely given to patients with stable chronic renal insufficiency or diabetes who are undergoing elective angiography.

Research: The authors did not state any explicit implications for research, but stated that the potential impact of NAC in acute settings has not been studied.

**Bibliographic details**


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**Other publications of related interest**


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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.