High-dose N-acetylcysteine for the prevention of contrast-induced nephropathy

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CRD summary
The authors concluded that high-dose N-acetylcysteine decreased the incidence of contrast-induced nephropathy. This was a generally well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy of high-dose N-acetylcysteine for the prevention of contrast-induced nephropathy.

Searching
MEDLINE was searched up to January 2008. Search terms were reported. MEDLINE daily update, MEDLINE in process and other non-indexed citations and Cochrane Central Register of Controlled Trials (CENTRAL) were searched on 29 February 2008. Abstracts of seven relevant meetings were searched from 2001 to 2007.

Study selection
Randomised controlled trials (RCT) that compared the effect of high-dose N-acetylcysteine administered immediately or within four hours of planned contrast exposure compared with a control group on incidence of contrast induced nephropathy in adults were eligible for inclusion. High dose was defined as a daily dose of more than 1,200mg or a single periprocedural dose of more than 600mg. Oral and intravenous routes were eligible for inclusion. Studies that used hydration were eligible if the same hydration regime was used in both the control and the intervention arms. Only English-language articles were eligible.

Included RCTs were of oral or intravenous N-acetylcysteine in doses that ranged from 1,800mg to 6,000mg in adult patients who underwent cardiac, peripheral or CT (computed tomography) scan imaging using iohexol, ioxilan, iopromide or iopamidol as a contrast agent. Most studies used oral N-acetylcysteine. In all studies, patients received concomitant hydration. The patients' average baseline serum creatinine ranged from 1.05mg/dL to 2.25mg/dL. Average patient age was 68 years, 38.7% were diabetic and 67.8% were male. The definition of contrast-induced nephropathy was an increase of 25% or more in serum creatinine or 0.5mg/dL. The time of defining contrast induced nephropathy ranged from 24 hours to 96 hours.

Two reviewers independently selected the studies for review. Disagreements were resolved by discussion.

Assessment of study quality
The validity of the included studies was assessed using the Delphi list, a nine-item checklist measuring allocation concealment, comparability of groups at baseline, inclusion criteria, placebo controls, blinding, intention-to-treat analyses and estimated variability of outcome. The Jadad scale, a three-item checklist measuring randomisation, blinding and withdrawal/dropouts (maximum score of 5) was also used.

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

Data extraction
Odds ratios (OR) with corresponding 95% confidence intervals (CI) and the overall incidence of contrast-induced nephropathy were extracted for each study. Outcomes at 48 hours were preferentially extracted. Authors were contacted for additional information.

Two reviewers independently extracted the data into pre-prepared excel spreadsheets. Disagreements were resolved by discussion.

Methods of synthesis
Pooled odds ratios with corresponding 95% CIs were calculated using the Mantel-Haenszel test and analysis was repeated using a random-effects model. Statistical heterogeneity was assessed using the Breslow-Day test and the $I^2$ statistic. Sensitivity analyses excluded the three studies in abstract form only, studies with a Jadad score less than 3 and...
included one small study available only in abstract form. Publication bias was assessed statistically using the Peters et al. modification of Macaskill's test and visually with a funnel plot.

**Results of the review**

Sixteen RCTs were included for the review (1,677 patients). It was not possible to allocate a Jadad score to the three studies published as abstracts. Four studies scored 4 or 5 on the Jadad scale, five scored 3 and four scored 1 or less. The main methodological weaknesses in the included studies were lack of or failure to describe allocation concealment, patient or care provider blinding and the use of intention-to-treat analyses.

N-acetylcysteine significantly reduced the risk of contrast-induced nephropathy compared to controls (OR 0.46, 95% CI 0.33 to 0.63). A sensitivity analysis that included only studies with a Jadad score of 3 or more continued to show a significant beneficial effect of N-acetylcysteine in preventing contrast-induced nephropathy (OR 0.34, 95% CI 0.22 to 0.52).

Sensitivity analyses that excluded studies available in abstract form or that included one small study available only in abstract form did not significantly alter the findings. There was no evidence of significant statistical heterogeneity or publication bias for any of these analyses.

**Authors' conclusions**

High-dose N-acetylcysteine decreased the incidence of contrast-induced nephropathy

**CRD commentary**

Inclusion criteria were clearly stated for intervention, study design and outcomes, but were broad for patients. Several relevant databases were searched. Attempts were made to identify unpublished data, thereby minimising the risk of publication bias; publication bias was assessed and no evidence of it found. Only English-language articles were eligible for inclusion, which introduced a risk of language bias. Appropriate steps were taken in the study selection and data extraction processes to minimise the risk of reviewer error and bias; it was unclear whether similar steps were taken in the validity assessment process, so potential bias could not be ruled out.

An appropriate quality assessment was performed; the quality of some included studies was low. A sensitivity analysis was performed using only high-quality studies. A suitable method was used to combine the studies. Statistical heterogeneity was assessed. Potential sources of heterogeneity were investigated.

This was a generally well-conducted study and the authors’ conclusions are likely to be reliable.

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

**Practice:** The authors stated that patients at risk of contrast-induced nephropathy should be administered N-acetylcysteine 1,200mg orally twice a day for 48 hours. Where the procedure was elective, dosing should commence the evening before contrast exposure. In emergencies, N-acetylcysteine should be started as soon as the decision to use contrast was made.

**Research:** The authors stated that further research was needed into the impact of N-acetylcysteine administered prophylactically to patients who underwent contrast exposure on other outcomes (such as mortality).

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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.