Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy

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CRD summary
The authors concluded that N-acetylcysteine was more renoprotective than hydration alone for reducing risk of contrast-induced nephropathy; theophylline may also reduce risk. In spite of some methodological issues with the review, the authors' conclusions were still likely to be reliable.

Authors' objectives
To determine the effects of N-Acetylcysteine, theophylline and other agents on preventing nephropathy.

Searching
MEDLINE, EMBASE, Web of Knowledge and The Cochrane Library were searched (dates ranged from 1966 to November 2006) for studies in English, French, German, Spanish or Italian; search terms were reported. Reference lists of identified articles were also searched.

Study selection
Randomised controlled trials (RCTs) that used intravenous iodinated contrast and which explicitly defined contrast-induced nephropathy and reported data to allow calculation of relative risk (RR) for the primary effect measure were eligible for inclusion. Studies had to have one treatment group receiving N-acetylcysteine, theophylline, fenoldopam, iloprost, statin, dopamine, trimetazidine, bicarbonate, ascorbic acid, furosemide or mannitol.

Most included studies evaluated patients with impaired renal function. All studies included patients with diabetes. The mean age of participants was over 65 years in around 80 per cent of studies. All studies reported contrast-induced nephropathy following elective radiographic procedures; most reported changes in serum creatinine at 48 hours. N-acetylcysteine was by far the most frequently used agent. Saline-only treatment was used as comparator in all studies. One reviewer selected studies for inclusion in the review.

Assessment of study quality
Study quality was assessed using the following criteria: allocation concealment; similarity of prognostic indicators at baseline; eligibility criteria; blinding (of patient, care provider, and outcome assessor); point estimates and measures of variability for primary outcomes; and use of intention-to-treat analysis. It appeared that two reviewers assessed study quality, with disagreements resolved by a third reviewer.

Data extraction
RRs and 95% confidence intervals (CIs) were calculated for contrast-induced nephropathy (the primary outcome). When data were missing the original authors were contacted for relevant information. Same-study dosage groups were considered to represent a single intervention to avoid double counting of shared control groups. Two reviewers separately extracted data according to a standardised form.

Methods of synthesis
A DerSimonian and Laird random-effects model was used to pool RRs. Subgroup analyses were conducted for each therapeutic regimen. Heterogeneity was assessed using the $I^2$ statistic (fixed-effect model) and by visual examination of forest plots. Meta regression was used to assess the effect of each study quality criterion on treatment efficacy. A funnel plot was used to assess publication bias, with the aid of an Egger precision-weighted linear regression test.

Results of the review
Forty-one RCTs were included in the review (n=6,379). Some studies had three treatment arms. Most studies (94 per cent) included participants with similar baseline characteristics, 51 per cent of studies blinded patients to treatment and 43 per cent blinded care providers, but only 6 per cent stated that outcome assessors were blinded and only 8 per cent used an intention-to-treat analysis. Only the characteristic of explicitly stating specific inclusion criteria (p=0.007)
independently contributed to heterogeneity across studies.

N-acetylcysteine significantly decreased risk of contrast-induced nephropathy compared with saline alone, 26 trials, RR 0.62, (95% CI: 0.44, 0.88, I²=55%). Furosemide use increased the risk for contrast-induced nephropathy, two trials, RR 3.27 (95% CI:1.48, 7.26, I²=0%). The effects of theophylline were not statistically significant. No evidence for significant publication bias was found.

Authors’ conclusions
N-acetylcysteine is more renoprotective than hydration alone for reducing risk of contrast-induced nephropathy; theophylline may also reduce risk.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies in five languages were undertaken by searching electronic databases and checking references. No search was made for unpublished data so this, coupled with the language restrictions, means that some relevant studies may have been missed. However, results from a funnel plot suggested publication bias was not a concern. Study quality was assessed and was used in interpreting the results of the review. Although suitable methods were used to minimise the risks of reviewer error and bias for the processes of study quality assessment and data extraction, only one reviewer selected studies for inclusion in the review, leaving this process open to such risks. Sufficient study details were provided and an appropriate meta-analysis of the data was undertaken. Although heterogeneity was assessed, its possible causes were not fully investigated or discussed. Many trials reported very few events, so a clear indication of the weight given to each study would have been useful in interpreting the pooling. The authors’ conclusions nevertheless reflected the evidence available and were likely to be reliable.

Implications of the review for practice and research
Practice: the authors stated that the use of agents such as N-acetylcysteine was reasonable in high-risk patients who were to receive large or repeated volumes of contrast agents.

Research: the authors stated that head-to-head studies of active agents should be undertaken to find the most effective regimen for preventing contrast-induced nephropathy.

Funding
National Institutes of Health, National Cancer Institute (grant 1 K07 CA108664 01A1), General Electric-Association of University Radiologists Radiology Research Academic Fellowship.

Bibliographic details

PubMedID
18283206

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetylcysteine /therapeutic use; Acute Kidney Injury /chemically induced /prevention & control; Ascorbic Acid /therapeutic use; Bicarbonates /therapeutic use; Clinical Trials as Topic /standards; Contrast Media /adverse effects; Furosemide /adverse effects; Protective Agents /therapeutic use; Research Design /standards; Theophylline /therapeutic use

AccessionNumber
12008008091
Date bibliographic record published
31/03/2009

Date abstract record published
15/04/2009

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.