Does the prophylactic use of N-acetylcysteine prevent contrast nephropathy in patients with renal insufficiency?

Birck R, Krzossok S, Markowetz F, Schnülle P, van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003;362:598-603.

Background: Contrast nephropathy, although in general a benign and reversible form of acute renal failure, is associated with increased in-hospital morbidity and mortality. Conflicting evidence exists in the literature with respect to the effectiveness of N-acetylcysteine (NAC), an antioxidative agent, for the prevention of contrast nephropathy.

Design: A meta-analysis including published, randomized, controlled trials compared the use of NAC with placebo in patients with chronic renal insufficiency receiving contrast media. The investigators searched electronic databases up to Feb. 5, 2003, with no language restrictions. Five years of proceedings from cardiology and nephrology meetings and references from identified papers were screened. The primary outcome was contrast nephropathy, defined as a 25% increase in serum creatinine from baseline levels or a rise in creatinine of 44.2 μmol/L or higher 48 hours after administration of contrast media.

Results: Seven studies (n = 805) that met the eligibility criteria were identified in the literature. All trials used standardized periprocedural fluid regimens and nonionic contrast. Mean baseline serum creatinine in the trials ranged from 123.76–247.52 μmol/L. Four of the 7 trials reported a significant risk reduction favouring NAC. Using a random-effects model, the pooled relative risk (RR) for contrast nephropathy in NAC versus usual care was 0.44 (95% confidence interval [CI] 0.22–0.88, p = 0.02). Sensitivity analysis performed by excluding the study with the largest effect size revealed no difference in either the magnitude or significance of the pooled risk reduction. The Q statistic suggested significant heterogeneity among the trials (p = 0.016), and the funnel plot revealed asymmetry, suggesting the presence of publication bias.

Commentary: This meta-analysis reveals significant beneficial effects of NAC to prevent contrast nephropathy in patients with chronic renal insufficiency. Strengths of this study include the use of a comprehensive search strategy, exclusion of nonrandomized studies and studies without appropriate control groups, use of 2 independent reviewers for searches and data extraction and the use of sensitivity analysis. Since publication of this meta-analysis, a number of additional trials that meet the same inclusion criteria have been published.[1–4] The majority of these trials show significant beneficial effects of NAC on contrast nephropathy, and the conclusion from this analysis remains robust even after inclusion of the single negative trial[3] (RR 0.51, CI 0.27–0.96, p = 0.036).

Despite the rigorousness of the meta-analysis, a number of limitations hamper the interpretation of this study. First, reasons for heterogeneity among the studies remain unknown and merit further exploration. Second, the presence of publication bias, suggested by the funnel plot, results in an overoptimistic RR. Third, whether prevention of a rise in serum creatinine translates into clinically meaningful end points, such as prevention of renal failure requiring dialysis, decrease in hospital stay or decrease in morbidity and mortality, remains unknown.

Practice implications: The use of NAC in patients with chronic renal insufficiency receiving contrast media prevents a rise in serum creatinine levels. As a relatively inexpensive and nontoxic therapy, the cost–benefit ratio likely favours its use. However, whether or not protection against a rise in creatinine confers any clinically significant benefit is unknown. Thus, the use of NAC should not replace other well-studied protective measures, such as an adequate intravenous fluid regimen consisting of 0.9% saline 12 hours before and after the procedure, use of low-osmolality contrast agents, limitation of the dose of contrast media and avoidance of concomitant nephrotoxic agents.

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References

1. Baker CS, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. *J Am Coll Cardiol* 2003;41(12):2114-8.
2. MacNeill BD, Harding SA, Bazari H, Patton KK, Colon-Hernadez P, de-Joseph D, et al. Prophylaxis of contrast-induced nephropathy in patients undergoing coronary angiography. *Catheter Cardiovasc Interv* 2003;60(4):458-61.
3. Boccalandro F, Amhad M, Smalling RW, Sdringola S. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. *Catheter Cardiovasc Interv* 2003;58(3):336-41.
4. Efrati S, Dishy V, Averbukh M, Blatt A, Krakover R, Weisgarten J, et al. The effect of N-acetylcysteine on renal function, nitric oxide, and oxidative stress after angiography. *Kidney Int* 2003;64(6):2182-7.

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