Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: a meta-analysis

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CRD summary
The review evaluated effectiveness of sodium bicarbonate versus normal saline for prevention of contrast-induced nephropathy and found sodium bicarbonate-based hydration to be superior to normal saline. The review had no major flaws, but the evidence implied that the authors’ conclusion could be more focused and that further research was needed to differentiate between different types of contrast.

Authors’ objectives
To evaluate the effectiveness of sodium bicarbonate versus normal saline for prevention of contrast-induced nephropathy.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, International Pharmaceutical Abstracts database and Google Scholar search engine were searched from 1990 to December 2008. Abstract lists and conference proceedings of American College of Cardiology, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, American Heart Association, American Society of Nephrology, European Renal Association, annual meetings of the Radiology Society of North America and World Congress of Cardiology were searched from 2007 to 2008. Published review articles, editorials and two internet sites were searched. The bibliography of each retrieved article was handsearched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that made a direct comparison of sodium bicarbonate versus pre-hydration with normal saline and that had contrast-induced nephropathy as a primary endpoint based on laboratory testing were eligible for inclusion. Secondary outcomes reported were mortality and need for dialysis. Studies were excluded if they were retrospective or if sodium bicarbonate was compared with normal saline plus N-acetyl cysteine. Contrast-induced nephropathy was defined differently by each included study, but was most commonly described as a 25% or more rise in serum creatinine within two to five days of contrast exposure. Other definitions used included an absolute increase of 0.5mg/dL serum creatinine and a composite definition of either a 25% increase or an absolute increase of 0.5mg/dL serum creatinine. There were both emergency and elective patients in the included studies. Where given, the proportion of participants with diabetes was 23.5% to 58.3%, mean age ranged from 47.7 to 75.5 years and proportion of males ranged from 50% to 90%. Where given, mean baseline creatinine level ranged from 0.89mg/dL to 1.99mg/dL. The contrasts used in the included studies included iopamidol, iodoxanol, iohexol, ioversol, ioxaglate, iohexol, iomeprol and ioxilan. Total dose of bicarbonate infused in included studies ranged from 9mL/kg to 24mL/kg versus a total dose of normal saline that also ranged from 9mL/kg to 24mL/kg. A range of 3mL/kg to 12mL/kg normal saline was infused prior to contrast.

Two independent researchers were involved in the literature search and study selection. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed by two reviewers. Criteria used included: concealment of allocation during randomisation; intention-to-treat analysis; and blinded assessment of outcome measures. The reviewers opted not to give a quality score.

Data extraction
Two reviewers performed data extraction. Data extracted included: clinical characteristics of the study population; laboratory data including baseline creatinine: amount of normal saline infusion in control group (total and before contrast administration); type of contrast and average contrast volume; and data on primary and secondary outcomes. Authors were contacted to obtain additional information. Data were used to calculate odds ratios (OR) and 95%
confidence intervals (CI) of the effect size of contrast-induced nephropathy for sodium carbonate compared to normal saline.

**Methods of synthesis**
Odds ratios were pooled using a random-effects model using intention-to-treat analysis. A continuity correction (Sankey et al.) was used when an event did not occur in one group. Between-study heterogeneity was determined using Q and $I^2$ tests, where a value of $I^2$ greater than 50% indicated at least moderate heterogeneity. Publication bias was assessed using the method of Egger et al., rank order correlation (Begg and Mazumdar) and visually using funnel plots. The effect of individual studies was assessed by omitting one study at a time from the pooled analysis. Fail-safe N was calculated (number of studies required to nullify the significant differences between the two groups) using the method of Rosenberg and Orwin. Since publication bias was found to be present, the Trim and Fill method (Duval and Tweedie) was used to calculate imputed odds ratios for contrast-induced nephropathy. A meta-regression was performed in order to find which covariates might be responsible for the heterogeneity of the analysis for contrast-induced nephropathy. A sensitivity analysis was carried out in order to assess the effect of certain characteristics using stratified analysis: patients treated with low osmolar versus iso-osmolar contrast; patients who underwent elective versus emergent procedures; published versus unpublished studies.

**Results of the review**
Seventeen relevant RCTs were identified (n=2,633, range 18 to 502). Eight RCTs were published in peer-reviewed literature and nine studies were unpublished at the time of the review. No quality details were provided for the included studies.

Sodium bicarbonate significantly lowered incidence of contrast-induced nephropathy compared to normal saline (OR 0.52, 95% CI 0.34 to 0.81, $I^2=48\%$, Q statistic=30.6). The number needed to treat to prevent one contrast-induced nephropathy was 16 (95% CI 10 to 34).

Stratified analysis found a stronger effect in patients who exclusively underwent emergency procedures (OR 0.10, 95% CI 0.02 to 0.42; two RCTs) compared with patients undergoing elective procedures (OR 0.63, 95% CI 0.43 to 0.92; 11 RCTs). Stratified analysis by type of contrast medium found a stronger effect of sodium bicarbonate versus normal saline for low-osmolar contrast media (OR 0.29, 95% CI 0.15 to 0.57; nine RCTs) compared to a non-significant effect for the pooled analysis of four RCTS that used iso-osmolar agent iodixanol. Published trials showed a stronger overall benefit of sodium bicarbonate (OR 0.40, 95% CI 0.21 to 0.76; eight RCTs) than with unpublished trials (nine RCTs), where the effect was not significant. Further analysis found that later trials tended to have a more modest benefit.

There was evidence for publication bias.

There was no significant difference between the sodium bicarbonate groups and the normal saline groups for the secondary outcomes: need for dialysis and mortality.

**Authors’ conclusions**
Sodium bicarbonate-based hydration was found to be superior to normal saline in prevention of contrast-induced nephropathy.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched and unpublished studies were considered, but it was unclear whether studies published in languages other than English were considered. Publication bias was assessed. Study quality was assessed using suitable criteria, but little of the resulting data was reported. Study selection was carried out with efforts to reduce error and bias; it was not reported whether this process applied to other aspects of the review process. Relevant study details were reported, but no details of length of follow-up or loss to follow-up were given. Statistical heterogeneity was assessed and there was evidence for some heterogeneity. The statistical method used for the meta-analysis of RCTs seemed appropriate. Sensitivity analyses were carried out and provided some useful information. The authors found evidence for publication bias with respect to studies that give significant results and investigated sources of heterogeneity. The review had no major flaws, but the evidence implied that the authors’ conclusions could be more focused.
Implications of the review for practice and research

Practice: The authors stated that sodium bicarbonate-based hydration should be considered the optimal method of hydration in high-risk patients who underwent treatment with iodinated contrast.

Research: The authors identified a need for further studies to assess interaction between type of contrast agent used and hydration strategy. The authors recommended further research that included larger studies on efficacy of use of a single bolus of sodium bicarbonate administered just prior to contrast, which would be easy to apply in most healthcare settings.

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