Meta-analysis of frusemide to prevent or treat acute renal failure
Ho K M, Sheridan D J

CRD summary
This review investigated the effects of frusemide intake to prevent or treat acute renal failure. The authors’ conclusion that frusemide is not effective in the prevention or treatment of acute renal failure in adults, and that high doses may be associated with an increased risk of ototoxicity, may be overstated given the small existing evidence base.

Authors’ objectives
To determine the efficacy and safety of frusemide for the prevention or treatment of acute renal failure in adults.

Searching
The Cochrane Controlled Trials Register (Issue 4, 2005) and MEDLINE and EMBASE (from inception to February 2006) were searched; the search terms were reported. In addition, the websites of the International Network of Agencies of Health Technology Assessment and International Society of Technology Assessment in Health Care were searched. The reference lists of relevant reviews and articles were also checked.

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 that compared frusemide with placebo were eligible for inclusion. Studies with a single dose of frusemide compared with prolonged continuous infusion were included in the review, whereas studies comparing two different modes of frusemide administration (e.g. regular bolus versus continuous infusion) were excluded. The doses of frusemide in the included studies were 1 or 2.5 mg/hour (intravenous infusion) or 80 mg (single intravenous bolus) in the prevention trials and 600 to 3,400 mg/day in the treatment trials.

Participants included in the review
Studies of adult patients treated for acute renal failure or its prevention were eligible for inclusion. The identified preventive studies included adult patients who had undergone cardiac surgery, cardiac angiography, and major general or vascular surgery; some included participants with mild pre-existing renal impairment. The majority of the treatment studies included adult patients with acute renal failure without chronic renal failure; one trial included patients with either acute renal failure or acute on chronic renal failure.

Outcomes assessed in the review
The studies had to report clinical end points to be eligible for inclusion. The primary outcomes included in-hospital mortality and the proportion of patients requiring renal dialysis or replacement therapy. The secondary outcomes were the proportion of patients remaining oliguric (defined as a urine output less than 500 mL/day), the proportion of patients who developed ototoxicity, the number of dialysis sessions required until recovery, and the length of hospital stay.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected papers for inclusion in the review.

Assessment of study quality
The methodological quality of the primary studies was assessed using the Jadad scale. In addition, randomisation, allocation concealment, blinding, withdrawals and intention-to-treat analysis were reported for each individual study. Allocation concealment was assigned a grade (adequate, uncertain or clearly inadequate) according to Cochrane.
Two reviewers independently assessed the quality of the primary studies.

**Data extraction**

Two reviewers independently extracted the data from the primary studies. The authors reported that there were no disagreements between reviewers on the data extracted. Relative risks (RRs) for categorical data and the weighted mean difference (WMD) for continuous data, along with their associated 95% confidence intervals (CIs), were extracted.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a meta-analysis using a random-effects model. Outcomes relating to in-hospital mortality and requirement for renal replacement therapy were stratified by the use of frusemide to prevent or to treat acute renal failure. Publication bias was assessed by funnel plot, using mortality as the clinical end point.

How were differences between studies investigated?
Statistical differences between the trials were assessed using the chi-squared test and I-squared statistic. Sensitivity analyses, including only trials that had adequate allocation concealment or excluding one study that compared a single dose of frusemide with continuous infusion, were performed.

**Results of the review**

Nine RCTs (n=849) were included in the review. Three trials used frusemide to prevent acute renal failure (325 enrolled) and six used frusemide to treat acute renal failure (623 enrolled).

Four trials received a Jadad score of 1, two trials received a score of 5, and the remaining three trials received scores of 4, 3 and 2. Four trials were judged to have adequate allocation concealment.

No significant reduction in in-hospital mortality (RR 1.11, 95% CI: 0.92, 1.33) was shown when frusemide was compared with placebo. When subgrouped by treatment trials (RR 1.09, 95% CI: 0.90, 1.31; based on 4 trials, n=574) and prevention trials (RR 2.33, 95% CI: 0.75, 7.25; based on 2 trials, n=202), frusemide was not shown to reduce in-hospital mortality in comparison with placebo.

No significant reduction in the requirement for renal replacement therapy (RR 0.99, 95% CI: 0.80, 1.22) was shown when frusemide was compared with placebo. Statistically significant heterogeneity was found because of differences in the treatment trials (P<0.0001). When subgrouped by treatment trials (RR 0.94, 95% CI: 0.71, 1.26; based on 4 trials, n=204) and prevention trials (RR 4.08, 95% CI: 0.46, 35.96; based on 3 trials, n=255), frusemide was not shown to reduce the requirement for renal replacement therapy in comparison with placebo.

No significant difference in the number of dialysis sessions required (WMD -0.48, 95% CI: -1.45, 0.50), or the proportion of participants with persistent oliguria (RR 0.54, 95% CI: 0.18, 1.61), was shown between frusemide and placebo. Statistically significant heterogeneity was found in the latter analysis. Frusemide was associated with an increase in hospital stay (WMD 3.57 days, 95% CI: 0.02, 7.12; P=0.049), based on 2 preventive studies. High-dose frusemide (1 to 3.4 g/day) was associated with an increased risk of deafness or tinnitus being reported (RR 3.97, 95% CI: 1.00, 15.78; P=0.05); no statistical heterogeneity was found.

Sensitivity analyses, including only studies with adequate allocation concealment or excluding the study using a single bolus of frusemide, did not change the magnitude or direction of the results obtained.

The absence of small studies showing a reduction in mortality after treatment with frusemide indicated a small possibility of publication bias.

**Authors' conclusions**
Frusemide is not effective in the prevention or treatment of acute renal failure in adults. High doses may be associated with an increased risk of ototoxicity.

**CRD commentary**

The review addressed a clearly stated question which was supported by relevant inclusion and exclusion criteria. Several electronic databases were searched without language restrictions, but a funnel plot analysis revealed the possibility of publication bias (although, rather unusually, demonstrating the absence of published positive studies). The procedures used to select papers for inclusion in the review and to extract the data were likely to minimise the possibility of error or bias. The methodological quality of the included studies was assessed. Individual results were reported, and the authors assessed and discussed the potential impact of aspects of methodological quality.

The quantitative analysis appeared appropriate and statistical heterogeneity was assessed. However, meta-analyses for outcomes relating to in-hospital mortality and the proportion of persistent oliguric patients after treatment for acute renal failure included participants in the control group that had been counted more than once; this might have affected the results obtained. In addition, the authors’ conclusions, which were largely based on small datasets from a small number of studies, may be overstated.

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

Practice: The authors did not state any implication for practice.

Research: The authors stated that the benefits of a particular dose or mode of administration are still uncertain.

**Funding**

Department of Intensive Care, Royal Perth Hospital.

**Bibliographic details**

Ho K M, Sheridan D J. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ 2006; 333: 420

**PubMedID**
16861256

**DOI**
10.1136/bmj.38902.605347.7C

**Original Paper URL**
http://www.bmj.com/content/333/7565/420

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Acute Kidney Injury /drug therapy /prevention & control; Adult; Diuretics /therapeutic use; Furosemide /therapeutic use; Humans; Randomized Controlled Trials as Topic

**AccessionNumber**
12006008373

**Date bibliographic record published**
31/12/2006

**Date abstract record published**
31/12/2006

**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.