A meta-analysis of continuous vs intermittent infusion of loop diuretics in hospitalized patients
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CRD summary
This review concluded that the continuous infusion of loop diuretics, preceded by a loading dose, resulted in greater diuresis than intermittent (bolus) infusion, for hospitalised adults with extracellular fluid volume expansion. Limitations to the quality of the evidence, the methods of synthesis, variation between trials, and the precision of the pooled results, suggest that these conclusions may not be reliable.

Authors' objectives
To compare the efficacy of continuous versus intermittent (bolus) intravenous loop diuretics for hospitalised patients with disorders associated with extracellular fluid volume expansion.

Searching
MEDLINE to October, 2012, and ClinicalTrials.gov were searched for studies published in any language. Search terms were reported. Abstracts from the annual meetings of the American Society of Nephrology were handsearched.

Study selection
Eligible studies were parallel-arm and crossover randomised controlled trials (RCTs) that compared the efficacy of continuous versus intermittent intravenous infusion of loop diuretics, for a minimum of four hours. Eligible trial populations were hospitalised children or adults with disorders causing extracellular fluid volume expansion. The primary outcomes of interest were the net changes in daily and hourly urine output (mL/day); secondary outcomes were stated.

The included trials were published between 1983 and 2011; most were of adults. Where reported, the mean age of adult patients ranged from 41 to 74 years; mean body weight ranged from 64kg to 85.4kg. The mean age of child patients ranged from 3.6 to 33.6 months; mean body weight ranged from 4.3kg to 14kg. Adult patients had chronic kidney disease, were critically ill in intensive care units, or were undergoing cardiac surgery; children were undergoing cardiac surgery. Nearly all trials used furosemide as the loop diuretic; one used bumetanide and one used torsemide. Interventions lasted from four to 112 hours for adults, and from 24 to 72 hours for children. The dose of furosemide (or equivalent dose) varied across the trials.

Two reviewers independently selected trials for inclusion.

Assessment of study quality
Trial quality was assessed using the Jadad Scale. Total scores ranged from 0 to 5, with 5 indicating high quality. The authors did not state how many reviewers assessed quality.

Data extraction
Data on the outcomes were extracted to calculate mean differences and relative risks, together with 95% confidence intervals. For crossover RCTs, only the data from the initial phase (before crossover) were extracted. A dose conversion factor (defined in the review) was used, where necessary.

The data were extracted independently by two reviewers; any discrepancies were resolved by consensus or with a third reviewer.

Methods of synthesis
The effect estimates and their 95% confidence intervals were pooled in meta-analyses (random-effects); these were performed separately for adult and child patients. Statistical heterogeneity was assessed using $I^2$ and Cochran’s Q. For the secondary outcome of mortality, for adults, a total of 0.5 was added to each result if there were zero events for either group.
Subgroup analyses of the primary outcome were performed according to predefined characteristics (stated in the review). Sensitivity analyses were performed by removing the two most extreme outlying trials. Meta-regression was performed to explore the relationship between treatment dose and the daily urine output.

Publication bias for trials of adult patients was assessed using funnel plots and Egger's test.

**Results of the review**

Eighteen RCTs were included in the review; 15 were of adults (749 patients, range eight to 308), and three were of children (92 patients, range 20 to 46). The overall quality of the trials was considered to be low (median 1). Most trials of adults scored 1 (range 1 to 5); those of children scored 1 or 2.

In the 14 trials of adults, continuous loop diuretic infusion resulted in an overall mean net increase in urine output of 334mL per day (95% CI -74 to 742) or 13.741mL per hour (95% CI -3.193 to 30.675) compared with bolus infusion, but these differences were not statistically significant. Statistical heterogeneity was high ($I^2=84\%$). The exclusion of two outliers resulted in a similar estimate of effect. A similar result was shown for daily urine output in trials of children (three RCTs; $I^2=65\%$).

In trials with a loading dose (10 RCTs), continuous infusion resulted in a statistically significant mean net increase of 294mL per day (95% CI 31 to 556) in daily urine output, compared with intermittent infusion. No statistically significant differences, between the two strategies, were found in any of the other subgroup analyses (reported in the review).

Compared with intermittent infusion, continuous infusion resulted in a statistically significant mean net decrease in body weight of 0.78kg (95% CI -1.54 to -0.03; three RCTs). No statistically significant differences were observed between the two strategies in in-hospital mortality, length of hospital stay, net changes in urinary sodium and potassium excretion rates, and net changes in levels of serum creatinine, sodium and potassium.

No evidence of a relationship between the furosemide-equivalent daily dose and daily urine output was observed. No evidence of publication bias was found.

**Authors’ conclusions**

Compared with intermittent infusion of loop diuretics, continuous infusion, preceded by a loading dose, resulted in greater diuresis in hospitalised adult patients with extracellular fluid volume expansion.

**CRD commentary**

The review question was clear and supported by reproducible inclusion criteria. Relevant data sources were searched for published and unpublished literature, and no language restrictions were imposed. The searching of only one database of published literature means that some relevant trials may have been missed. The processes of trial selection and data extraction were performed by two people; it was unclear whether quality assessment was performed in the same way, so the risk of reviewer error or bias cannot be ruled out.

The quality assessments suggested that most of the RCTs were of low quality. There was a substantial amount of statistical heterogeneity between the RCTs, with some clinical and methodological differences. This means that the decision to pool their data may not have been appropriate. The sources of heterogeneity were explored using appropriate methods. The confidence intervals, in the subgroup analyses and the meta-analysis, for daily urine output for adults, were large indicating some imprecision in the pooled estimates.

The authors' conclusions reflect some of the evidence presented; limitations to the quality of the evidence, the methods of synthesis, variation between trials, and the precision of the pooled results, suggest that these conclusions may not be reliable.

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

**Practice:** The authors did not state any implications for clinical practice.

**Research:** The authors stated that further research was required to examine whether continuous infusion of loop diuretics, preceded by a loading dose, had a clinical benefit for hospitalised patients.
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