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ORIGINAL

Continuous infusion versus bolus injection of furosemide in pediatric patients after cardiac surgery: a meta-analysis of randomized studies

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ABSTRACT

Introduction. Acute renal failure and fluid retention are common problems in pediatric patients after cardiac surgery. Furosemide, a loop diuretic drug, is frequently administered to increase urinary output. The aim of the present study was to compare efficacy and complications of continuous infusion of furosemide vs bolus injection among pediatric patients after cardiac surgery.

Methods. A systematic review and meta-analysis was performed in compliance with The Cochrane Collaboration and the Quality of Reporting of Meta-Analysis (QUORUM) guidelines. The following inclusion criteria were employed for potentially relevant studies: a) random treatment allocation, b) comparison of furosemide bolus vs continuous infusion, c) surgical or intensive care pediatric patients. Non-parallel design randomized trials (e.g. cross-over), duplicate publications and non-human experimental studies were excluded.

Results. Up to August 2008, only three studies were found, with 92 patients randomized (50 to continuous infusion and 42 to bolus treatment). Overall analysis showed that continuous infusion and bolus administration were equally effective in achieving the predefined urinary output, and were associated with a similar amount of administered furosemide (WMD=-1.71 mg/kg/day [-5.20; +1.78], p for effect=0.34, p for heterogeneity<0.001, I2=99.0). However, in the continuous infusion group, patients had a significantly reduced urinary output (WMD=-0.48 ml/kg/day [-0.88; -0.08], p for effect=0.02, p for heterogeneity <0.70, I2=0%).

Conclusions. Existing data comparing furosemide bolus injection with a continuous infusion are insufficient to confidently assess the best way to administer furosemide to pediatric patients after cardiac surgery. Larger studies are needed before any recommendations can be made.

Key words: furosemide, cardiac surgery, meta-analysis, intensive care unit, paediatric, acute kidney failure

Introduction

Acute renal failure and fluid retention are common problems in pediatric patients after cardiac surgery. (1,2) A positive fluid balance can further compromise cardiac and respiratory function. (3) Furosemide, a loop diuretic drug, is frequently administered to increase urinary output. Intravenous bolus injection is the traditional mode of administration to obtain a prompt, vigorous diuresis. However, many concerns have been raised about the large intravascular volume fluctuations that it may cause in an already labile circulatory system. (4) Continuous infusion of furosemide should allow better hemodynamic stability and fewer side effects together with easier achievement of the desired diuretic effect. Studies comparing con-

tinuous infusion and bolus injection have been performed in adult healthy volunteers, patients with chronic renal failure and patients with congestive hearth failure (CHF). (5-7) A recent review on the 2 modes of administration in CHF adult patients concluded that "the existing data still does not allow definite recommendations for clinical practice". (8) Randomized controlled trials in critically ill adult patients report conflicting results. (1, 9-11)

The aim of the present study was to compare efficacy and complications of continuous infusion of furosemide with those of bolus injection in pediatric patients after cardiac surgery.

Materials and Methods

Search Strategy

Pertinent studies were independently searched in PubMed (updated August 5th 2008) by two trained investigators (LC, GM). The full PubMed search strategy, including, as key-words, furosemide, bolus, infusion and perfusion, was developed according to Biondi-Zoccai et al. (12) and is available in the appendix. Recent conference proceedings (2006-2008), from the International Anesthesia Research Society, American Heart Association, American College of Cardiology, American Society of Anesthesiology and European Society of Cardiology, were hand or computer searched. In addition, we employed backward snowballing (i.e. scanning of references of retrieved articles and pertinent reviews). No language restriction was enforced, and non-English-language articles were translated before further analysis.

Study Selection

References obtained from database and literature searches were first independently examined at the title/abstract level by two investigators (LC, GM), with divergences resolved by consensus, and then, if potentially pertinent, retrieved as complete articles. The following inclusion criteria were employed for potentially relevant studies: a) random allocation to treatment, b) comparison of furosemide bolus vs continuous infusion, c) surgical or intensive care pediatric patients. The exclusion criteria were: a) non-parallel design randomized trials (i.e. cross-over), b) duplicate publications, c) non-human experimental studies d) no outcome data. Two investigators (LC, GM) selected studies for the final analysis by independently assessing compliance with selection criteria. Divergences from the selection criteria were resolved by consensus.

Data Abstraction and Study Characteristics

Baseline, procedural and outcome data were independently abstracted by two investigators, with divergences resolved by consensus. Specifically, we extracted study design (including patient selection and randomization), population, clinical setting. At least two separate attempts at contacting original authors were made in case of missing data.

The primary end-point of our analysis was to determine if the two methods of administration were equally effective. Secondary end-points included the incidence of acute kidney injury (AKI), serum creatinine levels, survival, and the duration of intensive care unit (ICU) and hospital stay.

Internal Validity Assessment

Internal validity and risk of bias of included trials was appraised according to The Cochrane Collaboration methods and by completing a risk of bias table. This was performed by two independent co-authors (GL, GB-Z), with divergences resolved by consensus. (13-15)

Data Analysis and Synthesis

Statistical heterogeneity and inconsistency was measured using, respectively, Cochrane Q tests and I2. (16) Statistical significance was set at the two-tailed 0.05 level for hypothesis testing and at the 0.10 for heterogeneity testing. According to Higgins et al., (15) I2 values around 25%, 50% and 75% were considered representing respectively low, moderate and severe statistical inconsistency. Weighted means differences (WMD) and 95% CI were computed for continuous variables, using a fixed effect method for I2 values$<$50% and a random effect method for I2 values$>$50%. The risk of small studies bias (including publication bias) was assessed by visual inspection of funnel plots. (17) Unadjusted P values are reported throughout. Computations were performed with RevMan 4.2 (a freeware available from The Cochrane Collaboration). The study was performed in compliance with The Cochrane Collaboration and the Quality of Reporting of Meta-Analysis (QUORUM) guidelines.

Results

Database searches, snowballing and contacts with experts yielded a total of 157 citations (figure 1). Excluding 149 non-pertinent titles or abstracts, we retrieved, in complete form and assessed according to the selection criteria, eight studies. A total of five studies were further excluded because of their non-experimental design, including the use of historical controls, or because of duplicate publication. We finally identified three eligible randomized clinical trials, (18-20) which were included in the final analysis (table 1, column 1).

Study Characteristics

The three included trials randomized 92 patients (50 to continuous infusion and 42 to bolus treatment). All trials were performed in pediatric ICU patients following cardiac surgery. All authors tailored the drug dosage in an attempt to reach a pre-established urinary output in both groups (1ml/kg/h). Patients' severity scores were not reported in any

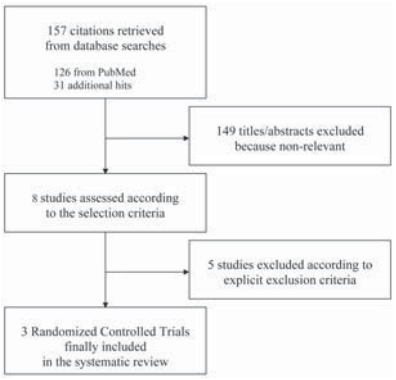

Figure 1. Flow chart of randomized controlled studies.

Table 1. Characteristics, results and conclusions of three studies randomizing cardiac surgery pediatric patients after cardiopulmonary bypass to receive a continuous infusion (C group) or a bolus (B group) administration of furosemide.

Author, Journal, Year	Inclusion criteria	Exclusion criteria	Age C-group (years)	Age B-group (years)	Serum creatinine C-group (mg/dl)	Serum creatinine B-group (mg/dl)	Patients with renal failure	Pre-bolus administered at beginning in C-group (mg/kg)	Pre-bolus administered at beginning in B-group (mg/kg)	Urine volume / furosemide - C-group	Urine volume / furosemide - B-group	Authors' conclusions
Singhm Crit Care Med, 1992	--normovolemia --urinary output <1ml/kg/h	--electrolitic abnormalities --other diuretics	2,3+2,2	1,4+1,4	NR	NR	NR	0,1	1	32,1+17 ml/mg	51,2+19,2 ml/mg	--infusion requires less furosemide --continuous infusion gives more predictable urinary output --less electrolitic abnormalities
Klinge, Intensive Care Med, 1997	--pediatric ICU setting after open heart surgery	--hemodynamic instability --dopamine more than 10mcg/kg/min --epinephrine --norepinephrine >0,3mcg/kg/min	3,4+3,1	2,4+2,1	0,4+0,1	0,3+0,06	0	0	0	1,0 + 0,4 ml/kg/h/mg furosemide	0,5 + 0,2 ml/kg/h/mg furosemide	--Bolus requires less furosemide to get same urinary output --continuous infusion gives more predictable urinary output
Luciani, Ann Thorac Surg, 1997	--more than 6 months old; --cardiac surgery within 6 hours --post-operative hemodynamic instability	--electrolitic abnormalities --other diuretics	3,7+3,4	1,8+2,5	0,5+0,4	0,5+0,2	0	0,1	1	not reported	not reported	--infusion requires less furosemide

NR, not reported.

of the studies. Patients were balanced as per age and baseline serum creatinine levels. Patients' characteristics, studies' results and authors' conclusions are reported in table 1.

Quantitative Data Synthesis

Overall analysis showed that both continuous infusion and bolus administration achieved a urinary output > 1 ml/kg/hour in all patients, and continuous infusion and bolus administration were associated with similar amounts of furosemide administered to achieve the desired urinary output. (Mean for continuous group: 2.1; mean for bolus group 3.1; WMD=-1.71 mg/kg/day [-5.20; +1.78], p for effect=0.34, p for heterogeneity<0.001, I2=99.0%) (figure 2).

In the continuous infusion group, patients had a significantly reduced urinary output. (Mean for continuous group 2.4; mean for bolus group 2.7; WMD=-0.48 ml/kg/day [-0.88; -0.08], p for effect=0.02, p for heterogeneity <0.70, I2=0%) (figure 3).

No data on the incidence of AKI, serum creatinine levels after treatment, survival rates, and the duration of ICU and hospital stay were reported. Two authors reported that no complication was observed during the study period.

We also appraised the robustness and validity of our findings by exploring the likelihood of small study bias by means of funnel plot inspection. We found no major evidence of such bias for either total furosemide dose or urine output.

Discussion

Currently available data from three small and relatively heterogeneous studies were insufficient to assess the merits of the two modes of furosemide administration in pediatric patients after cardiac surgery.

Diuretic treatment is widely used in ICU to resolve fluid overload or to treat (or prevent) AKI; furosemide is the most commonly prescribed drug, at least for AKI patients. (21) Nevertheless, administration of loop diuretics in adult patients seems not to be associated with clinical benefits in the treatment or prevention of AKI, as three recent reviews pointed out. (22-24) Mehta and co-workers (25) showed that diuretics administrations in critically ill patients with AKI is associa-

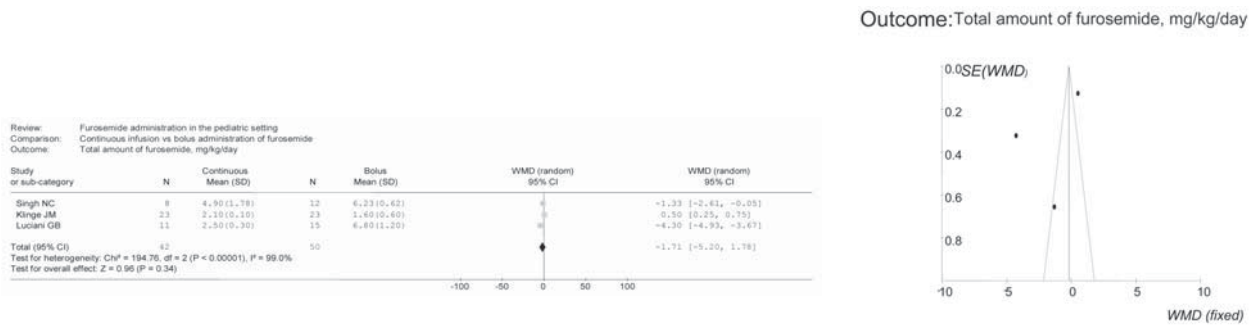

Figure 2. Forest plot for pooled estimates (A) and funnel plot for small study bias appraisal (B) for total use of furosemide.

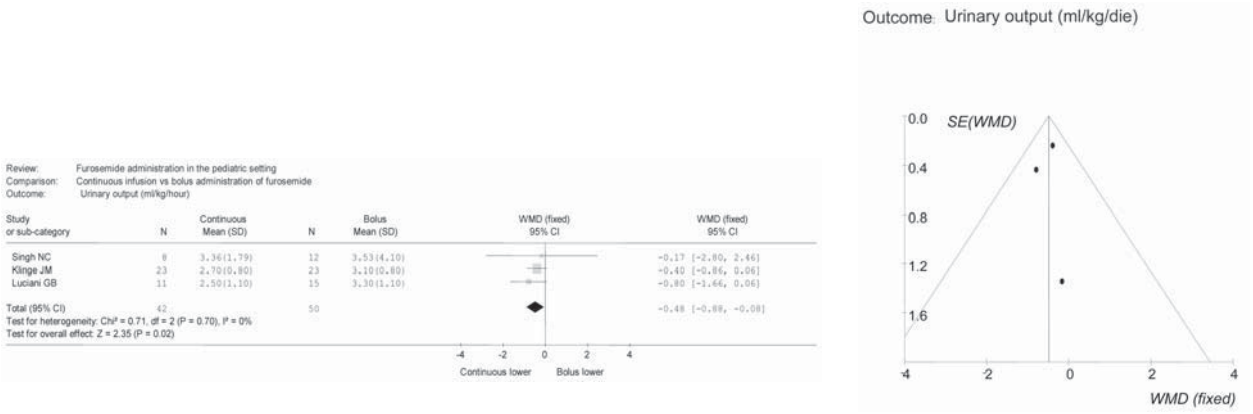

Figure 3. Forest plot for pooled estimates (A) and funnel plot for small study bias appraisal (B) for total urinary output.

ted with an increased risk of death and non-recovery of renal function. Other authors did not report higher mortality associated with diuretics. (21-23) Only fenoldopam seems to be associated with an improved perioperative outcome in adult patients with or at risk for acute renal failure, like critically ill patients or those undergoing major surgery, (26) especially cardiac surgery. (27)

Pharmacodynamic studies suggest that continuous infusion may be the most effective way to administer loop diuretics. (28) Loop diuretics act on the thick ascending loop of Henle, promoting natriuresis and consequently diuresis. Their receptor is on the internal surface of the tubular lumen. The delivery time of loop diuretics to the action site, within the lumen, appears to determine the diuretic response more than the total drug dose or its mode of administration. (29,30) The most efficient drug excretion rate in terms of maximal sodium excretion (and diuretic response as well) can be determined: (29) using continuous infusion, urinary furosemide excretion rate will be closer to the most efficient excretion rate over a longer period. (7) Two other mechanisms could contribute to the superior efficacy of a continuous infusion: acute drug tolerance is less pronounced, (31) and the drug-free interval during which sodium-retaining mechanisms act is shorter. (7)

Continuous infusion of furosemide should have a better safety profile, allowing better hemodynamic stability and fewer side effects like ototoxicity. (7)

Despite the wide use of furosemide and the fact that continuous infusion intuitively seems superior to bolus injections, evidence on this topic is still lacking. Randomized controlled trials in adults have focused on patients with CHF. A Cochrane review on the mode of administration of loop diuretics in this sub-group of patients found eight studies involving 254 patients. Continuous infusion appeared to obtain greater diuresis, and to reduce mortality, hospital stay and ototoxicity; however, as the same authors stated, the poor quality of data could not allow making robust recommendations for clinical practice. (8)

Martin published an excellent review of the literature on continuous infusion of loop diuretics in critically ill patients more than ten years ago, but a meta-analysis was never performed. (28)

Studies on paediatric patients are very limited. Only three controlled, randomised clinical trials have compared the two modes of administration in criti-

cally ill pediatric patients after cardiac surgery.

Our meta-analysis showed that continuous infusion and bolus administration were associated with similar amounts of administered furosemide.

No major outcome was reported. Furthermore, the three studies included in this meta-analysis had conflicting results. Probably, the most important reason was the heterogeneity of the included population in terms of hemodynamic stability. In the study by Luciani, (20) hemodynamic instability was an inclusion criteria, while in Klinger's (19) it was an exclusion criteria. In Singh's study, (18) the cardiac indices and the percentage of patients requiring inotropes suggest that hemodynamic stability was quite common in the study population. As a matter of fact, Luciani reported a marked variability of hourly urine output in the bolus group, with a significant greater need for fluid replacement and higher (even if not significantly different) fluctuations of central venous pressure (CVP) and heart rate in this group. Similar results were also reported by Copeland in adult patients after cardiac surgery. (4)

No treatment failure was reported, indicating that both treatments proved effective as the desired urinary output was obtained (even though patients in the continuous infusion group had a reduced urinary output). Toxicity was not different between the two modes of administration, despite the hemodynamic lability of these patients: the typical sophisticated continuous monitoring in this setting could have avoided major problems. Even in Luciani's unstable study population, (19) hemodynamic profile, during the research, is defined adequately in both groups. Very large doses were not used during the studies, and this can explain the absence of ototoxicity.

Moreover, adverse events rate is low with high dosage of furosemide. Ho et al. (21) in a recent review on adult patients reported an ototoxicity rate of 3.5%. A 10% change of incidence, with an alpha value of 0.05 and a power of 0.8 would require about 350 patients to be detected, far above the sample size of examined studies.

Evidence-based recommendations for critically ill pediatric patients after cardiac surgery cannot be formulated. Continuous infusion resulted in a gentle and sustained diuresis, likely the best way to eliminate fluid overload at least in hemodynamically unstable patients according to the authors of all the three analysed studies. Bolus administration is effective, but intravascular volume shifts can be pronounced.

It should be noted that in critically ill adults the importance of applying a protocol, to drive furosemide therapy, appeared superior than the chosen mode of administration: Schuller (11) reported that the nonrandomized (excluded for lacking informed consent or unavailability of the research staff) twelve patients who met inclusion criteria and did not meet exclusion criteria had a smaller cumulative furosemide dose, less net diuresis, and a longer ICU and hospital stay than randomized patients. Protocol-guided fluid management was also adopted and recommended by other authors. Randomized studies comparing protocol-driven and non-standardized furosemide administration in critically ill paediatric patients are warranted.

Limitations. The limitations of systematic reviews and meta-analyses are well known and include the level of uniformity among study populations as well as the primary endpoints in each study. (32)

All the studies appeared of suboptimal quality, as testified by the common lack of details on the method used for randomized sequence generation and allocation and absence of blinding, and thus at risk of moderate bias.

An additional limitation of our study is that no important outcomes were reported. Nonetheless, our results provide the most comprehensive and thorough comparison of furosemide bolus versus continuous infusion in pediatric critically ill patients after cardiac surgery.

Conclusion

Existing data comparing furosemide bolus injection or continuous infusion are insufficient to confidently assess the best mode of administration for pediatric patients after cardiac surgery. Both methods were effective in achieving the desired urinary output, and safe. Larger studies are needed before recommendations can be made.

APPENDIX

(bolus AND (infus* OR perfusio*) AND (furosemide OR frusemide OR diuretic* OR diuresis)) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt]))

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