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Continuous infusion versus bolus injection of furosemide in critically ill patients. A systematic review and meta-analysis

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ABSTRACT

Introduction. Fluid overload and a positive fluid balance are common in the intensive care unit (ICU). Furosemide is frequently administered to increase urine output. A bolus injection is the traditional mode of administration, but many concerns have been raised about possible intravascular volume fluctuations, toxicity and enhanced tolerance. Furosemide related adverse effects can be enhanced in critically ill patients. Continuous infusion should allow better hemodynamic stability, less side effects and an easier achievement of the desired diuretic effect. We performed a systematic review and meta-analysis to compare the effects and complications of continuous furosemide infusion with those of bolus injections in critically ill patients in the ICU.

Methods. Studies were searched in PubMed (updated January 2009). Backward snowballing of included papers was performed. International experts were contacted for further studies.

The inclusion criteria were: random allocation to treatment, comparison of furosemide bolus vs continuous infusion, performed in surgical or intensive care patients. The exclusion criteria were: non-parallel design randomized trials, duplicate publications, non-human experimental studies, no outcome data.

Results. Four eligible randomized clinical trials were identified, including 129 patients (64 to continuous infusion and 65 to bolus treatment). Continuous perfusion was not associated with a significant reduction in risk of mortality as compared to bolus injection

Conclusions. Furosemide in continuous perfusion was not associated with a significant reduction in risk of hospital mortality as compared to bolus administration in critically ill patients in ICU, but existing data are insufficient to confidently assess the best way to administer furosemide . Applying a protocol to drive furosemide therapy could be more relevant than the chosen mode of administration.

Key words: furosemide, kidney Failure, intensive care, drug therapy, meta-analysis, diuretics

Introduction

Fluid overload is a common problem in critically ill patients of intensive care units (ICU); a positive fluid balance is often associated with a poor outcome. (1-4) Furosemide, a loop diuretic drug, is frequently administered to increase urinary output. Intravenous bolus injection is the traditional mode of administration to obtain prompt, vigorous diuresis. However, many concerns have been raised about possible marked intravascular volume fluctuations, toxicity and enhanced tolerance. (5,6)

Theoretically, continuous infusion of furosemide should allow better hemodynamic stability and less side effects, together with an easier achievement of the desired diuretic effect. Studies comparing continuous infusion and bolus injection have been undertaken in healthy volunteers, patients with chronic renal failure, children after cardiac surgery and patients with congestive heart failure (CHF). (7-10) A recent review of the 2 modes of administration in CHF patients concluded that "the existing data still does not allow definite recommendations for clinical practice". (11)
Furosemide related adverse effects can be enhanced in critically ill patients: their labile circulatory system can be markedly affected by intravascular volume depletion; besides that, electrolyte imbalance must be avoided. As a matter of fact, diuretic administration in critically ill patients with acute renal failure (ARF) has been associated with an increased risk of death and non-recovery of renal function. (12)
The aim of the present study was to compare effects and complications of continuous infusion of furosemide with those of bolus injections among critically ill patients in the ICU.

Materials and methods

Search Strategy Pertinent studies were independently searched in PubMed (updated January 2009) by two trained investigators. The full PubMed search strategy, including the keywords furosemide, bolus, infusion and perfusion, was developed according to Biondi-Zoccai et al. (13) and is available in the appendix. In addition, we used backward snowballing (i.e. scanning of reference of retrieved articles and pertinent reviews) and we contacted international experts for further studies. 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, 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) performed in surgical or intensive care patients. The exclusion criteria were: a) non-parallel design (i.e. cross-over) randomized trials, b) duplicate publications, c) non-human experimental studies d) no outcome data. Two investigators 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.
The primary end-point of our analysis was to determine whether a continuous infusion of furosemide reduced hospital mortality as compared to bolus administration.
Data Analysis and Synthesis
Binary outcomes from individual studies were analyzed according to the Mantel-Haenszel model in order to compute individual odds ratios (OR) with pertinent 95% confidence intervals (CI), and a pooled summary effect estimate was calculated by means of fixed effects model. (14) Statistical heterogeneity and inconsistency was measured using, respectively, Cochrane Q tests and I2. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing and at the 0.10 for heterogeneity testing. I2 values around 25%, 50% and 75% were considered representing respectively low, moderate and severe statistical inconsistency. Unadjusted P values are reported throughout. Computations were performed with SPSS 11.0 (SPSS, Chicago IL, USA) and 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 (QUOUM) guidelines.

Results

Database searches, snowballing and contacts with experts yielded a total of 157 citations (figure 1). Excluding 148 non-pertinent titles or abstracts, we retrieved nine studies in complete form and assessed them according to the selection criteria. A total of five studies were further excluded because of their non-experimental design, including the use of historical controls, or because of duplicate publications. We finally identified four eligible randomized clinical trials, (14-17) which were included in the final analysis
Study Characteristics
The four included RCTs (randomized controlled trials) randomized 129 patients (64 to continuous infusion and 65 to bolus treatment). All trials were performed on ICU patients. Three out of four authors tailored the drug dosage in an attempt to reach a pre-established urinary output in both groups. Patients were balanced as per age and baseline serum creatinine levels. Characteristics and results of the analyzed studies, and author's conclusions, are reported in table 1; patients' characteristics are reported in table 2. Administered furosemide dosages, urine outputs, complications and length of stay in ICU in continuous and bolus groups are summarized in table 3.
Quantitative Data Synthesis
Overall analysis showed that furosemide in continuous perfusion was not associated with a significant reduction in the risk of mortality (6/55 [11.9%] in the continuous infusion group vs 10/56 [17.8%] in the bolus arm, OR=0.60 [0.20-1.84], p for effect=0.37, p for heterogeneity=0.91, I^2=0%) (figure 2). The studies appeared of suboptimal quality, as testified by the common lack of details on the method used for randomization sequence generation and allocation. No RCT employed a multicenter design, a feature that does not strictly impact on internal validity but usually increases external validity of a trial.

Discussion

Currently available data from four small

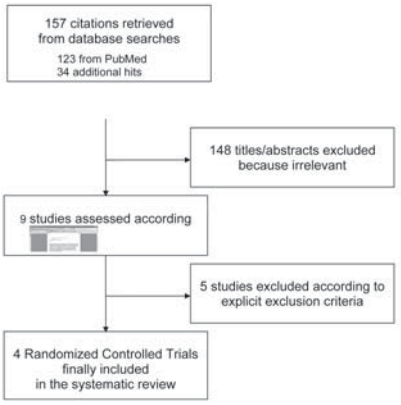

Figure 1. Flow-chart of the retrieved studies.

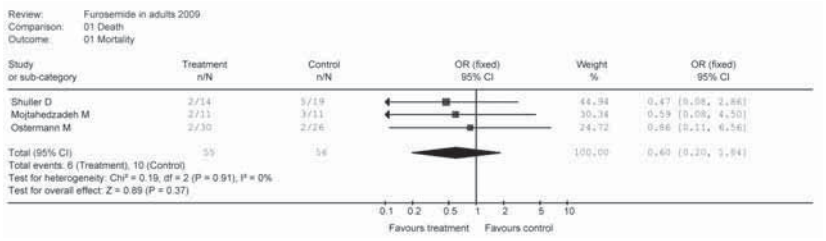

Figure 2. Forest plot of analyzed studies for risk of mortality. Overall analysis showed that furosemide in continuous perfusion was not associated with a significant reduction in the risk of mortality.

and relatively heterogeneous studies were insufficient to assess the merits of the two modes of furosemide administration in critically ill adult patients. Hospital mortality does not appear to differ.

Diuretic treatment is widely used in ICU to resolve fluid overload or to treat (or prevent) ARF; furosemide is by far the most commonly prescribed drug, at least for ARF patients. (18) In patients with acute lung injury, furosemide shortens mechanical ventilation and ICU stay, without ameliorating mortality. (19) In contrast, administration of loop diuretics in adult patients is not associated with clinical benefits in the treatment or prevention of ARF, as two recent reviews pointed out. (20-21) Mehta and co-workers showed that diuretic administrations in critically ill patients with ARF is associated with an increased risk of death and non-recovery of renal function. (12) Other authors did not report higher mortality associated with diuretics. (18)

The best mode of furosemide administration, bolus injection vs. continuous infusion, remains to be demonstrated. Pharmacodynamic studies suggest that continuous infusion may be the most effective way to administer loop diuretics. (22) 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 drug total dose or than its mode of administration. (23,24) The most efficient drug excretion rate in terms of maximal sodium excretion (and diuretic response as well) can be determined (23) using continuous infusion- urinary furosemide excretion rate will be closer to the most efficient excretion rate over a longer period. (10) Other two mechanisms could contribute to the superior efficacy of continuous infusion: acute drug tolerance is less pronounced, (6) and the drug-free interval during which sodium-retaining mechanisms act is shorter. (10)

Continuous infusion of furosemide should have a better safety profile, allowing better hemodynamic stability

Table 1. Characteristics and results of the analyzed studies, and author's conclusions.

Author (ref)	Journal, year	Setting	N (continuous group)	N (bolus group)	Experimental design	Conclusion
Copeland JC (17)	American J of Surgery, 1984	Intensive Care Unit after cardiac surgery	9	9	fixed dose (0,6 mg/kg) in 2 boluses or continuous perfusion	Non significant difference at the end of the study, but more vigorous hourly urinary output in bolus group
Schuller D (16)	Crit Care Med, 1997	Pulmonary oedema in Intensive Care Unit	14	19	variable dose of furosemide to reach a predetermined output	No difference
Mojtahedzadeh M (15)	J of Infusion Nursing, 2004	Intensive Care Unit	11	11	variable dose of furosemide to reach a predetermined output	No difference
Ostermann M (14)	Nephron Clin Pract, 2007	Intensive Care Unit	30	26	variable dose of furosemide to reach a predetermined output	Continuous infusion requires less furosemide

Table 2. Patients' characteristics of the analyzed studies. APACHE II: Acute Physiology and Chronic Health Evaluation II score.

Author	Age, continuous group	Age, bolus group	Basal serum creatinine, continuous group, mg/dl	Basal serum creatinine, bolus group, mg/dl	APACHE II, continuous group	APACHE II bolus group
Copeland JC (17)	not reported	not reported	not reported	not reported	not reported	not reported
Schuller D (16)	67 ± 15	67 ± 15	1.9 ± 1.10	2.3 ± 2.30	14 ± 5	15 ± 7
Mojtahedzadeh M (15)	not reported	not reported	1.8 ± 0.15	1.5 ± 0.19 mg/dl	18 ± 2.1	20 ± 1.5
Ostermann M (14)	60 ± 3.3	60 ± 3.3	1.4 ± 0.14	1.5 ± 0.12	20 ± 1.2	19 ± 1.3

Table 3. Administered furosemide dosages, urine output, complications and length of stay (LOS) in intensive care unit (ICU) in continuous and bolus Groups.

Author	mean (SD) dose continuous group	mean (SD) dose bolus group	urine volume/ furosemide continuous group	urine volume/ furosemide bolus group	mean (±SD) urinary output (ml) continuous group	mean (±SD) urinary output (ml) bolus group	complications	LOS (mean ±SD) in ICU continuous group	LOS (mean ±SD) in ICU bolus group
Copeland JC (17)	0.05/mg/kg/h	0.3 mg/h in 2 boluses	not reported	not reported	1870 ± 752 /24h	2673 ± 925 /24h	none	not reported	not reported
Schuller D (16)	not reported	not reported	not reported	not reported	not reported	not reported	2 in bolus group	not reported	not reported
Mojtahedzadeh M (15)	not reported	not reported	not reported	not reported	not reported	not reported	1 in bolus group	not reported	not reported
Ostermann M (14)	9.2 ± 5.05 mg/h for 24h	24.1 ± 19.26 mg/h for 24h	31.6 ml/mg	18 ml/mg	5400 (SD not reported) /24h	5300 ml (SD not reported) /24h	not reported; said no differences	15.4 ± 17.9 day	8,9 ± 8,68 day

and less side effects, such as ototoxicity. (10)

Despite the wide use of furosemide and the fact that continuous infusion intuitively seems superior than bolus injection, we lack evidence on this topic. Randomized controlled trials have focused on patients with congestive heart failure. A Cochrane review on the mode of administration of loop diuretics in this sub-group of patients found eight studies involving 254 patients. Studies were heterogeneous in terms of study population, dose, duration of the infusion, presence or absence of a loading dose. 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 robust recommendations for clinical practice. (11)

Very few controlled, randomised clinical trials have compared the two modes of administration in critically ill adult patients in the ICU setting. Martin published an excellent review of the literature more than ten years ago, but a meta-analysis was never performed. (22) In ICU, patients' hemodynamic lability and latent ARF are balanced by intensive monitoring and rapid correction of imbalances, so it is difficult to predict if the differences between furosemide continuous infusion and bolus injection are minimized or emphasized in this setting. 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 (25) reported that a subgroup of non-randomized (excluded for lacking of informed consent or unavailability of the research staff) patients in his study had less cumulative furosemide dose, less net diuresis, and longer ICU and hospital stay than randomized patients.

Conclusions

Furosemide in continuous perfusion was not associated with a significant reduction in risk of mortality as compared to bolus administration in critically ill patients hospitalised in ICU, but existing data are insufficient to confidently assess the best way to administer furosemide .

APPENDIX

Search strategy for PubMed, developed according to Biondi-Zoccai et al. (13)

(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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