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Intermittent administration of furosemide versus continuous infusion in the postoperative management of children following open heart surgery

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Abstract *Objective:* To compare the amount of furosemide needed to fulfil defined criteria for renal output if given intermittently or as a continuous infusion and to compare the effect of these two regimens on hemodynamic variables and urine electrolyte concentrations.
Design: Prospective randomized study of postoperative hemodynamically stable pediatric cardiac patients. The patients were given furosemide according to the urine output, either as an intermittent bolus injection or as a continuous infusion.
Setting: Pediatric intensive care unit in a university hospital
Patients: The patients were randomly assigned before admission to either the intermittent i. v. or the continuous furosemide i. v. infusion group.
Measurements and results: Demographic and hemodynamic data were recorded for a maximum of 72 h, as were furosemide dose, urine output, and fluid and inotropic drug requirements. Forty-six patients completed the study. Maximal hourly urine output was significantly higher in the intermittent group. A significantly lower dose of furosemide in the intermittent group produced the same 24-h urine volume as in the continuous infusion group.
Conclusions: Intermittent furosemide administration may be recommended in hemodynamically stable postoperative pediatric cardiac patients because of less drug requirement. However, the high maximal urine output may cause hemodynamic problems in patients who depend on high inotropic support.

Key words Furosemide · Infusion vs intermittent injection · Urine output · Cardiac surgery · Intensive care · Pediatrics

Introduction

Furosemide is frequently given to patients following open heart surgery, but controlled clinical trials are rare. In a review of the literature, Martin and Danzinger reported on only three controlled trials comparing continuous infusion of furosemide with an intermittent bolus injection [1].

In 1983, Copeland et al. described 18 adult post-open heart surgery patients. They found no significant difference in urine output between a continuous infusion and an intermittent bolus injection of furosemide. But patients treated with the continuous infusion showed a more controlled and physiologic diuresis compared to the intermittent group [2].

Singh et al. supported these findings in a pediatric cohort [3]. Their intermittent group received a minimum of 1 mg/kg of intravenous furosemide every 4 h, resulting in a daily dose of $\geq$ 6 mg/kg. The continuous infusion group was given a minimum of 0.1 mg/kg · h, resulting in a lower daily dose of $\geq$ 2.4 mg/kg. The patients in the intermittent group received a significantly higher dose of furosemide than those in the continuous infusion group. The urine output values in the two groups

Table 1 Doses of furosemide according to urine output

Urine output	Intermittent group	Continuous group
Starting of the study period if	urine output < 1 ml/kg · h	
Starting dose	0.5 mg/kg BW	2 mg/kg BW · day
< 6 ml/kg BW · 6 h (< 1 ml/kg BW · h) and CVP < 5 cm H_2O	0.5 mg/kg BW and 10 ml/kg BW fluid	2 mg/kg BW · day and 10 ml/kg BW fluid
< 6 ml/kg · 6 h (< 1 ml/kg BW · h) and CVP ≥ 5 cm H_2O	1 mg/kg BW	4 mg/kg BW · day
≥ 6 ml < 12 ml/kg BW · 6 h (≥ 1 ml < 2 ml/kg BW · h)	0.5 mg/kg BW	2 mg/kg BW · day
≥ 12 ml < 18 ml/kg BW · 6 h (≥ 2 ml < 3 ml/kg BW · h)	0.25 mg/kg BW	1 mg/kg BW · day
≥ 18 ml/kg BW · 6 h (≥ 3 ml/kg BW · h)	No furosemide	No furosemide

were similar and the continuous furosemide group showed less urinary loss of sodium and chloride. The authors concluded that a continuous i. v. infusion of furosemide is advantageous in postoperative pediatric cardiac patients, when compared to intermittent furosemide administration.

The third study was reported only in abstract form. The authors found a significantly greater average urine output in the continuous infusion group compared with the bolus injection group [4].

Other investigators studied the effect of continuous infusion versus bolus injection of furosemide in patients with congestive heart failure [5, 6]. Continuous infusion resulted in greater diuresis [5], and weight loss and relief of symptoms were observed in patients resistent to intermittent administration of furosemide [6]. However, all studies were performed with either a fixed dose of furosemide in both groups [2, 4–6] or with a higher dose in the intermittent group [3]. These dose regimens may have contributed to the advantages seen with the continuous infusion of furosemide. Therefore, we conducted a prospective clinical trial using a study protocol based on furosemide doses calculated according to the urine output.

Patients and methods

The study population consisted of pediatric patients with congenital heart defects who were treated after cardiac surgery in our intensive care unit. The study protocol had been reviewed and approved by local authorities. The patients were randomly assigned before admission to either the intermittent i. v. (group 1) or the continuous i. v. infusion group (group 2). The patients were reviewed after admission to the unit. Patients who were hemodynamically unstable, requiring high doses of dopamine (> 10 μg/kg per min) and/or adrenaline or noradrenaline (> 0.3 μg/kg per min) were excluded from the study. All patients were treated according to the following guidelines: total fluid intake was 40 ml/m^2 body surface · h on the day of surgery and 60 ml/m^2 body surface · h on the following days. Electrolytes were administered according to serum electrolyte values: if potassium levels fell below 40 mmol/l, 1 mmol/kg BW i. v. potassium was given. The patients received antibiotic prophylaxis with cefuroxime 100 mg/kg body weight.

The study period started when the urine output fell below < 1 ml/kg per h. If central venous pressure (CVP) was < 5 cm H_2O, indicating deficient intravascular volume, 10 ml/kg of the maintenance fluid (glucose 5 %) was administered. If CVP was > 5 cm H_2O, the patient was given the first dose of furosemide. Patients who were assigned to group 1 received 0.5 mg/kg furosemide. In group 2 we started a continuous infusion of 2 mg/kg per day. If the urine output remained > 1 ml/kg per h and < 3 ml/kg per h during the study period, the dose of furosemide was adjusted according to the study protocol (Table 1). In the case of a urine output < 1 ml/kg per h or > 3 ml/kg per h, the dose was adjusted immediately. The maximal duration of the study period was 72 h.

Demographic data and baseline variables recorded included age, weight, congenital heart defect, surgical procedure, number and amount of additional fluids administered, and potassium intake after the first dose of furosemide. The following variables were measured before and at regular intervals during the study period: CVP, hourly urine output, serum electrolyte values, including serum creatinine, at least twice a day, and urinary electrolyte values once a day.

The following parameters were calculated: maximal decrease of CVP (CVP before furosemide/minimal CVP after furosemide), urine output related to furosemide administration [urine output (ml/day)/furosemide (mg/day)] and loss of potassium related to furosemide administration [potassium (mmol/day)/furosemide (mg/day)].

Demographic and baseline variables are represented as means ± SD. Differences between the groups were determined using the Wilcoxon test for nonrelated parameters. Statistical significance was inferred with $p < 0.05$.

Results

Fifty-seven patients were enrolled into the study. Two patients had to be excluded after surgery because of postoperative hemodynamic instability, and 9 patients did not require furosemide during the study period.

Table 2 Results for both intermittent and continuous administration of furosemide

	Intermittent group	Continuous group	*p* value
Urine output (ml/kg BW · h)			
Day 1	3.1 ± 0.8	2.7 ± 0.8	NS
Day 2	2.9 ± 1.1	2.9 ± 0.9	NS
Day 3	2.9 ± 1.0	3.6 ± 1.1	NS
Furosemide dose (mg/kg BW · d)			
Day 1	1.6 ± 0.6	2.1 ± 0.7	0.014
Day 2	0.9 ± 0.5	1.7 ± 0.6	0.0003
Day 3	1.0 ± 0.5	1.7 ± 1.0	0.014
Urine output/furosemide dose (ml/mg)			
Day 1	51.2 ± 19.2	32.1 ± 17.6	0.03
Day 2	62.5 ± 20.9	41.1 ± 13.3	0.002
Day 3	67.9 ± 25.6	46 ± 20.5	0.041
Urine maximal (ml/kg BW · h)	15.8 ± 3.7	9.4 ± 4.1	< 0.0001
Urine minimal (ml/kg BW · h)	0.3 ± 0.2	0.5 ± 0.3	NS
Urinary potassium (mmol/l urine)			
Day 1	541.2 ± 262.4	500.0 ± 109.5	NS
Day 2	389.2 ± 203.8	559.1 ± 225.7	NS
Day 3	228.3 ± 177.9	307.5 ± 266.5	NS
Urinary potassium/furosemide dose (mmol/l urine · mg furosemide)			
Day 1	438.5 ± 380.7	284.6 ± 170.2	NS
Day 2	472.9 ± 394.4	350.9 ± 198.1	NS
Day 3	237.6 ± 202.1	101.4 ± 110.6	NS
Potassium intake (mmol/kg BW · d)			
Day 1	1.4 ± 0.86	1.6 ± 0.7	NS
Day 2	1.5 ± 0.7	3.0 ± 4.4	NS
Day 3	1.5 ± 0.8	1.4 ± 0.8	NS

Therefore, 46 patients were treated according to the study protocol. Twenty-three patients were randomly assigned to the intermittent group and 23 patients were given a continuous infusion of furosemide.

The distribution of diagnoses in both groups was similar (intermittent group listed first): atrial septal defect 6 vs 5; ventricular septal defect 4 vs 2; tetralogy of Fallot 4 vs 3; atrioventricular canal 4 vs 4; aortic stenosis 1 vs 1; coarctation 1 vs 1; aorto-pulmonary window 1 vs 0; pulmonary stenosis 1 vs 0; single ventricle 1 vs 0; double-chambered right ventricle 0 vs 2; double-outlet right ventricle 0 vs 3; mitral insufficiency 0 vs 1. In the intermittent group (group 1) 7 infants and 15 children were treated compared to 6 infants and 16 children in group 2. There were no significant differences in the two groups regarding age (group 1, 2.4 ± 2.1 years vs 3.4 ± 3.1 years in group 2), weight (10.8 ± 5.7 vs 14.5 ± 9.3 kg), CVP before (7.5 ± 2.2 vs 8.4 ± 2.7 mm Hg) and after furosemide (4.6 ± 2.7 vs 4.6 ± 3.3 mm Hg), and the dose of dopamine (1.93 ± 0.98 vs 1.26 ± 0.86 μg/kg per min). There was no significant difference between the two groups regarding serum creatinine values before and during the study period (creatinine level before surgery: 0.3 ± 0.06 mg/dl, minimum 0.2 mg/dl, maximum 0.4 mg/dl vs 0.4 ± 0.1 mg/dl, minimum 0.2 mg/dl, maximum 0.5 mg/dl; highest creatinine value during the study period: 0.3 ± 0.1 mg/dl, minimum 0.2 mg/dl, maximum 0.5 mg/dl vs 0.4 ± 0.1 mg/dl, minimum 0.2 mg/dl, maximum 0.7 mg/dl). The measured and calculated values are displayed in Table 2.

In both groups, 18 patients needed additional volume administration during the study period (cf. Table 3). Furosemide had to be increased in 5 patients in both groups; in group 1 the furosemide dose was lowered in 17 patients versus only 8 patients in group 2. The maximal furosemide dose was 3.5 mg/kg BW · day in group 1 and 3.8 mg/kg BW · day in group 2, respectively. Furosemide therapy was stopped in 1 patient in both groups on day 2 of the study period.

The patients in the intermittend group needed a significantly lower daily dose of furosemide. As the urinary output values in the two groups were similar, the urine output per mg furosemide in the intermittent group was significantly higher when compared to the continuous infusion group.

The minimal hourly urine output was not different in the two groups. The maximal hourly urine output, however, was significantly higher in the intermittent group than in the continuous infusion group.

Discussion

Our results seem to be contradictory to most of the studies comparing intermittent administration to continuous infusion of furosemide. However, all the studies pub-

Table 3 Comparison of additional fluid administration in the two groups

	Intermittent group	Continuous group	*p* value
Day 1			
10 ml/kg BW	7	8	
20 ml/kg BW	5	7	
30 ml/kg BW	1	0	
> 30 ml/kg BW	3	2	
Median (ml/kg BW)	10	10	NS
Mean (ml/kg BW)	17.9	13.4	NS
Maximum (ml/kg BW)	100	40	
Day 2			
10 ml/kg BW	7	6	
20 ml/kg BW	0	2	
30 ml/kg BW	3	1	
Median (ml/kg BW)	0	0	NS
Mean (ml/kg BW)	6.1	5.7	NS
Maximum	30	30	
Day 3			
10 ml/kg BW	0	1	
20 ml/kg BW	4	0	
Median (ml/kg BW)	0	0	
Mean (ml/kg BW)	5.7	0.8	NS
Maximum	20	10	NS

lished so far were performed with either a fixed dose of furosemide in both groups [2, 4–6] or with a higher dose in the intermittent group [3].

We tried to adjust the dose of furosemide to the patient's need instead of administering a fixed dose. Intermittent administration of furosemide resulted in a significantly lower daily dose of furosemide over the study period (3 days) and the dose was significantly more effective. One might argue that the algorithm was not followed in the group with continuous infusion, as a urine output of 2.7–3.6 ml/kg BW per h should have resulted in a furosemide dose of 1 mg/kg BW per day (cf. Tables 1, 2). Our patients, however, received 1.7–2.1 mg/kg BW per day (cf. Table 2). Although the cause of this discrepancy is not completely clear, it may be that the the lower concentration of furosemide at the tubular receptor during the continuous infusion attenuates the effectiveness of the administered dose. This is supported by the study by Copeland et al. [2], who administered very low doses of 1.2 mg/kg BW and did not see any difference in the effectiveness of a continuous infusion versus a bolus injection of furosemide. On the contrary, others who used markedly higher doses of furosemide saw greater effectiveness with a continuous infusion of furosemide [3, 7].

In a prospective cross-over trial on patients with congestive heart failure by Lahav et al., low doses of 90–120 mg/day were used [5]. They found greater diuresis and natriuresis when administering a continuous infusion of furosemide following a single loading dose. But they used a fixed dose of furosemide in both groups and the bolus injection was given every 8 h regardless of the hourly urine output. In a prospective study, Green et al. measured the serum half-life ($t_{1/2}$) of furosemide and found it to be approximately 70 min in healthy children and 120 min in children with congestive heart failure (CHF), with great interindividual variations (17–249 min in children with CHF and 54–110 min in children without heart disease) [8]. The time interval of 8 h reported by Lahav et al. may be more than $10 \times t_{1/2}$, resulting in an almost complete loss of furosemide activity.

After one single dose of furosemide, diuresis peaks within 1 to 2 h [5]. In patients who receive a continuous infusion of furosemide without a loading dose, the diuretic response may be delayed for several hours, as reported by Copeland et al. [2]. This might explain the lower activity of furosemide on the first day of our study. But as we required a higher dose of furosemide during continuous infusion on the following days as well, the clinical significance of this delay does not seem to be important.

Mean fluid intake was higher in the intermittent bolus group, but this was not statistically significant (cf. Table 3). Furthermore, the difference was mainly caused by one patient who required 100 ml/kg BW of additional volume because of low blood pressure. Therefore, we believe that this difference did not influence our results.

Acute adverse effects of furosemide therapy are uncommon. Supraventricular tachycardia associated with continuous infusion of high dose furosemide (0.75–1 mg/kg BW · h), caused by a rapid fluid shift in the intravascular volume produced by furosemide administration and drug-related fever have been reported [9, 10].

We did not see any severe adverse effects. Blood pressure was stable during the study period and no arrhythmias occurred.

We think that small doses of furosemide may be sufficient to maintain good renal function in the hemodynamically stable patient. In these patients, intermittent diuretic therapy with furosemide may be more effective than continuous infusion if the doses are adjusted according to the hourly urine output.

As others have found [3, 5], we found greater variability in urine output in the intermittent group than in the continuous infusion group. But CVP was not significantly different in the two groups during the study period, indicating hemodynamic stability.

We conclude that intermittent therapy with furosemide may be recommended for the hemodynamically stable postoperative pediatric cardiac patient. Patients who are hemodynamically unstable should be given a continuous infusion because of the more predictable urine output.

References

1. Martin SJM, Danzinger LH (1994) Continuous infusion of loop diuretics in the critically ill: a review of the literature. Crit Care Med 22: 1323–1329
2. Copeland JG, Campbell DW, Plachetka NW, Salomon NW, Larson DF (1983) Diuresis with continuous infusion of furosemide after cardiac surgery. Am J Surg 146: 796–799
3. Singh NC, Kissoon N, al Mofada S, Bennett M, Bohn DJ (1992) Comparison of continuous versus intermittent furosemid administration in postoperative pediatric patients. Crit Care Med 20: 17–21
4. Wilbur RL, Riemersma LJ (1990) Comparison of furosemide administration by bolus or constant infusion in critically ill patients. ASHP Midyear clinical meeting abstracts 25: 310E
5. Lahav M, Regev A, Raànani P, Theodor E (1992) Intermittent administration of furosemide vs. continuous infusion preceded by a loading dose for congestive heart failure. Chest 102: 725–731
6. Meyel van JJM, Smits P, Dormans T, Gerlag PGG, Russel FGM, Gribnau FWJ (1994) Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance. J Intern Med 235: 329–334
7. Krasna JM, Scott GE, Scholz PM, Spotnitz AJ, Amckenzie JW, Penn F (1986) Postoperative enhancement of urinary output in patients with acute renal failure using continuous furosemide therapy. Chest 89: 295
8. Green TP, Mirkin BL (1982) Determinants of the diuretic response to furosemide in infants with congestive heart failure. Pediatr Cardiol 3: 47–51
9. Wilson NJ, Aderly RJ, McEniery LA (1991) Supraventricular tachycardia associated with continuous furosemide infusion. Can J Anaesth 38: 502–505
10. Glegg HW, Riopel DA (1995) Furosemide-associated fever. J Pediatr 126: 817–818