Continuous Versus Intermittent Furosemide Infusion in Critically Ill Infants After Open Heart Operations

Giovanni Battista Luciani, MD, Sanjiv Nichani, MB, Anthony C. Chang, MD, Winfield J. Wells, MD, Christopher J. Newth, MB, and Vaughn A. Starnes, MD

Divisions of Cardiothoracic Surgery and Pediatric Intensive Care, Childrens Hospital Los Angeles, Los Angeles, California

Background. **Use of intravenous furosemide is generally avoided in critically ill neonates and infants soon after open heart operations to prevent fluctuations in intravascular volume and resulting circulatory instability.**

Methods. **To assess and compare the safety and efficacy of continuous versus intermittent intravenous furosemide, we undertook a prospective, randomized trial in 26 consecutive patients less than 6 months of age. Inclusion criteria were presence of low-output syndrome requiring inotropic support (24/26 patients) or pulmonary hypertension requiring vasodilator therapy (10/26 patients) within 6 hours of discontinuation of cardiopulmonary bypass. Eleven patients received 0.1 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} continuous intravenous furosemide (group 1) and 15 received 1 mg/kg bolus every 4 hours (group 2) for 24 hours. Mean age (3.7 ± 3.4 versus 1.8 ± 2.5 months) and weight (4.6 ± 2.1 versus 4.3 ± 1.7 kg) were comparable.**

Results. **Group 2 infants showed slightly greater absolute urinary output (2.5 ± 1.1 mL/kg per hour versus 3.3 ± 1.1 mL/kg per hour, $p = 0.05$). However, urinary output per dose of drug was significantly larger in group 1 infants (1.0 ± 0.4 versus 0.5 ± 0.2 mL $\cdot$ kg^{-1} $\cdot$ h^{-1}; $p = 0.002$) with lesser fluctuations (variance, 1.9 ± 1.6 versus 3.8 ± 2.1; $p = 0.02$) and fluid replacement needs (20.6 ± 3.8 versus 51.8 ± 14.4; $p = 0.001$). Electrolyte replacement requirements were similar. A trend toward greater hemodynamic instability in group 2 patients (heart rate variance 88.4 ± 79.8 versus 128.3 ± 82.7; $p = 0.09$; central venous pressure variance 2.8 ± 1.90 versus 4.1 ± 3.7; $p = 0.07$; mixed venous oxygen saturation variance, 32.3 ± 27.6 versus 45.7 ± 20.4; $p = 0.06$) was noted. All patients who completed the study protocol survived operation and were discharged home.**

Conclusions. **We conclude that (1) commonly used doses of both intermittent and continuous intravenous furosemide infusion can be safely administered to critically ill neonates and infants as early as 6 hours after operation, (2) continuous infusion yields an almost comparable urinary output with a much lower dose of furosemide, and (3) intermittent administration is associated with greater fluctuations in urinary output and greater needs for fluid replacement therapy.**

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The use of cardiopulmonary bypass (CPB) for open heart operations in neonates and infants has been associated with a systemic inflammatory response and multiple organ dysfunction, a condition known as postperfusion syndrome [1, 2].

Renal insufficiency, as manifested by oliguria and fluid retention, is relatively common after pediatric cardiac operations and affects 5% to 30% of children operated on with the aid of CPB [3, 4]. The resulting fluid overload often compromises the already precarious cardiac and pulmonary function, leading to further hemodynamic instability and need for prolonged mechanical ventilatory support.

Several agents have been used for their ability to treat postoperative oliguria and fluid retention, including low-dose dopamine infusion, loop diuretics, and mannitol. However, because of the often labile circulatory conditions of neonates and infants after open heart operations and the tendency of bolus loop diuretics to cause acute fluctuations in intravascular volume, furosemide administration is generally avoided in the immediate postoperative course.

The use of furosemide as a continuous intravenous infusion has been shown to produce a more controlled diuresis in the adult patient undergoing cardiac surgical procedures [5]. Preliminary reports suggest that it may prove as effective in adult patients who are hemodynamically compromised but stable after open heart operations [6]. Currently, little information has been obtained on the effects of continuous intravenous furosemide infusion in the pediatric patient [7].

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Address reprint requests to Dr Luciani, Division of Cardiac Surgery, University of Verona, O. C. M. Piazzale Stefani 1, Verona, 37126 Italy.

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The purpose of the present study was to define and compare the safety and efficacy of continuous versus intermittent furosemide infusion in neonates and infants who are hemodynamically unstable soon after open heart operations.

Patients and Methods

Patients

At Childrens Hospital Los Angeles, a prospective, randomized clinical trial comparing the effects of continuous and intermittent bolus furosemide administration was approved by the Committee for Clinical Investigations and it was undertaken on all consecutive patients between January 1, 1995, and February 28, 1995, for whom informed consent had been obtained from the parents.

Inclusion criteria were the coexistence of (1) age at operation less than 6 months; (2) reparative or palliative cardiac surgical procedure performed with the aid of CPB; (3) early (within 6 hours of CPB discontinuation) postoperative hemodynamic instability; (4) normal ($\geq$3.5 mmol/L) serum potassium concentration; and (5) no administration of any diuretic during the operation and within 6 hours of CPB discontinuation. Hemodynamic instability was defined as (1) low-output syndrome with poor peripheral perfusion (capillary refill time $\geq$3 seconds), normal central venous pressure greater than or equal to 6 to 8 mm Hg, metabolic acidosis (≤ -3 base excess), low mixed venous O_2 saturation less than or equal to 55%, and oliguria (<1 mL $\cdot$ kg^{-1} $\cdot$ h^{-1}), requiring high-dose ($\geq$10 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} dopamine or dobutamine, or need for epinephrine infusion) inotropic support, or (2) pulmonary hypertension (systolic pulmonary artery to systemic arterial pressure ratio $\geq$0.75) requiring intravenous or inhaled (nitric oxide) vasodilator therapy, or (3) both.

All patients fulfilling the above criteria were randomly assigned to receive either continuous furosemide infusion (group 1) or intermittent bolus therapy (group 2). The study was begun 6 hours after weaning from CPB and continued for the following 24 hours.

Conduct of Cardiopulmonary Bypass

Because the weights of the infants were comparable, ranging from 2.4 to 7.1 kg, bypass prime composition and conduct of extracorporeal perfusion were identical in the two groups. Prime solution was composed of 1 unit of packed red blood cells (250 to 300 mL), 1 unit of fresh frozen plasma (200 to 250 mL), 25% albumin (100 to 150 mL), plasmalyte-A (100 to 200 mL), heparin (3 units/mL), sodium bicarbonate (15 to 25 mEq), mannitol (0.5 g/kg), phenytoin (5 mg/kg), and calcium chloride (1.0 mg/mL of packed red blood cell). No diuretics were administered during bypass. Perfusion flow was kept at 100 to 150 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} for rectal temperatures ranging 36° to 24°C, and at 50 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} for temperatures between 24° and 20°C. Deep hypothermic arrest was induced at rectal temperatures of 18°C or lower. Mean perfusion pressure was maintained between 30 and 45 mm Hg in neonates (<1 month) and between 40 and 60 mm Hg in infants (<6 months).

Methods of Furosemide Administration

GROUP 1 (CONTINUOUS FUROSEMIDE INFUSION). The patients were given an initial dose of 0.1 mg/kg intravenous furosemide (minimum of 1 mg) and then continuous intravenous infusion was started at 0.1 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}. This infusion rate was doubled every 2 hours (to a maximum of 0.4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) if the urinary output (UO) was less than 1 mL $\cdot$ kg^{-1} $\cdot$ h^{-1} in the 4 previous hours of observation. The concentration of the drug was 2 mg/mL (200 mg/100 mL 5% dextrose in water) infused at an initial rate of 0.05 mL/kg of body weight per hour (0.1 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}). The infusion syringe and the intravenous catheter line were screened against light to prevent the tendency of furosemide to discolor.

GROUP 2 (INTERMITTENT FUROSEMIDE BOLUS ADMINISTRATION). The patients were given 1 mg/kg of furosemide intravenously every 4 hours. The dose was increased by 0.25 mg/kg intravenously to a maximum of 2 mg/kg intravenously, if the UO was less than 1 mL $\cdot$ kg^{-1} $\cdot$ h^{-1} in the previous 4 hours of observation. The drug was administered undiluted (10 mg/mL) during 1 to 2 minutes.

The starting dose of furosemide administered during the study was different in the two patient groups due to a deliberate methodologic choice. There were two primary reasons for electing to expose the infants to two different starting doses of furosemide: (1) These selected doses are the commonly recommended and prescribed quantities for intravenous furosemide bolus and continuous infusion therapy, respectively. The first goal of the study was to assess the safety and efficacy of these currently recommended doses in neonates and infants. To render the starting dose of drug given in the two groups comparable, group 1 infants should have received a dose of 0.4 mg/kg every 4 hours (total dose, 2.4 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}). We anticipated that this dosage would have risked promoting diuresis to an unsatisfactory low level for the first 24 hours postoperatively, possibly slowing significantly recovery in this group of patients. The decision to respect the currently prescribed doses of furosemide was thus taken both on clinical and on ethical grounds. (2) A previous prospective, randomized clinical trial comparing efficacy and safety of continuous versus intermittent furosemide administration in children after open heart operations used the above reported doses [7]. To allow for comparison of results, the study design needed to be similar.

Demographic and Clinical Variables

Demographic and clinical data recorded included age, weight, preoperative therapy with furosemide, preoperative serum creatinine concentration, surgical procedure, aortic cross-clamp and bypass time, postoperative inotropic support, intravenous or inhaled vasodilators, life-threatening arrhythmias, presence of open sternotomy wound, total chest tube output, and total fluid intake and

electrolyte intake during the study period. The following variables were measured before (baseline) and at regular time intervals during the study: UO, heart rate, central venous pressure, systemic blood pressure, and pulmonary artery pressure, hourly; urinary and serum electrolytes every 6 hours; and mixed venous O_2 saturation, every 12 hours.

Statistical Analysis

Variables were reported as means ± standard deviation. Differences between continuous variables were analyzed using the two-tailed nonpaired Student's *t* test, whereas differences between distributions were assessed using the Pearson's χ^2 test. For each patient the average of 24 observations of UO, heart rate, central venous pressure, mean blood pressure, and mean pulmonary artery pressure, five observations of urinary and serum electrolytes, and three observations of mixed venous O_2 saturation were summarized as means ± standard deviation and compared between the two groups using the two-tailed nonpaired Student's *t* test. To assess variability of the clinical and hemodynamic parameters between groups, we calculated the variances ± the standard deviation and compared them using the two-tailed nonpaired Student's *t* test. Statistical significance was inferred with a value of p less than 0.05.

Results

Patients

Twenty-nine neonates and infants satisfied the requirements for enrollment in the study during a 2-month period. Two patients could not be enlisted because of lack of parental consent. In addition, 1 neonate with hypoplastic left heart syndrome, who had been randomly assigned to group 2 (intermittent bolus), died 3 hours after receiving the first dose of furosemide (1 mg/kg) and could not be included in the analysis of results. There was clinical evidence that the demise was caused by pulmonary hyperperfusion and it was thus unrelated to the administration of the drug.

Twenty-six patients completed the study protocol and could be used for comparison of the two treatment protocols. Analysis of the demographic and clinical variables of the patient population revealed no differences in terms of preoperative age, weight, or need for preoperative furosemide administration (Table 1). The preoperative diagnoses were transposition of the great arteries in 7 patients, ventricular septal defect or atrial septal defect in 6, complete atrioventricular septal defect in 3, pulmonary atresia with intact ventricular septum in 2, interrupted aortic arch, ventricular septal defect, and subaortic stenosis in 2, and, total anomalous pulmonary venous connection, tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus communis, single ventricle with restrictive bulboventricular foramen, and hypoplastic left heart, each in 1 patient. Surgical repair was performed in the neonatal period in 7 of 11 (64%) group 1 versus 10 of 15 (67%) group 2 infants. A detailed list of the specific operative procedures in the two groups is reported in Table 2. The aortic cross-clamp and CPB times were comparable. One neonate in group 1 (9%) and 2 in group 2 (13%) needed a period of deep hypothermic circulatory arrest for aortic arch repair. Prestudy clinical conditions were comparably critical in the two groups: the vast majority of infants required postoperative intravenous inotropic support, although this proportion was higher in group 2, whereas a similar percentage of patients returned to the intensive care unit with an open sternotomy wound and were on intravenous vasodilator drugs because of hemodynamic instability. In two patients, one in each group, with a history of prolonged intubation because of bronchopulmonary dysplasia and who presented with severe pulmonary hypertension after repair of large ventricular septal defect, therapy with inhaled

Table 1. Patient Demographic and Clinical Data[a]

Variable	Continuous (n = 11)	Intermittent (n = 15)	*p* Value
Age (mo)	3.7 ± 3.4	1.8 ± 2.5	0.1
Weight (kg)	4.6 ± 2.1	4.3 ± 1.7	0.7
Preop furosemide (% pts)	73	80	0.3
Preop creatinine (mg/dL)	0.5 ± 0.4	0.5 ± 0.2	0.6
Aortic cross-clamp (min)	42.5 ± 6.5	53.6 ± 10.5	0.09
CPB (min)	59.8 ± 26.2	72.8 ± 29.7	0.07
Open sternotomy (% pts)	27	33	0.3
Inotropes (% pts)	91	100	0.006
IV vasodilators (% pts)	36	40	0.8
Inhaled NO (% pts)	9	7	0.7
Arrhythmias (% pts)	9	13	0.4

[a] Data are shown as mean ± standard deviation where appropriate.

CPB = cardiopulmonary bypass; IV = intravenous; NO = nitrous oxide; Preop = preoperative; pts = patients.

Table 2. Operative Procedures

Operation	Continuous (n = 11)	Intermittent (n = 15)
TAPVC repair	...	1
VSD/ASD patch	5	1
AVSD two-patch	...	3
ToF transanular patch	1	...
RVOT patch + BT	2	...
ASO	2	5
DORV repair	...	1
Truncus repair	...	1
IAA/VSD/SAS repair	...	2
BCPC + DSK	...	1
Norwood	1	...

ASD = atrial septal defect; ASO = arterial switch operation; AVSD = atrioventricular septal defect; BCPC = bidirectional cavopulmonary connection; BT = Blalock-Taussig; DORV = double-outlet right ventricle; DSK = Damus-Stansel-Kay; IAA = interrupted aortic arch; RVOT = right ventricular outflow tract; SAS = subaortic stenosis; TAPVC = total anomalous pulmonary venous connection; ToF = tetralogy of Fallot; VSD = ventricular septal defect.

Table 3. Diuretic Effect and Fluid Balance[a]

Variable	Continuous (n = 11)	Intermittent (n = 15)	*p* Value
Dose (mg · kg^{-1} · day^{-1})	2.5 ± 0.3	6.8 ± 1.2	0.001
UO (mL · kg^{-1} · h^{-1})	2.5 ± 1.1	3.3 ± 1.1	0.05
UO (mL · kg^{-1} · h^{-1})/mg drug	1.0 ± 0.4	0.5 ± 0.2	0.0017
UO variance	1.9 ± 1.6	3.8 ± 2.1	0.02
Na^+ intake (mmol/day)	3.1 ± 1.2	3.2 ± 1.4	0.6
Cl^- intake (mmol/day)	3.1 ± 1.2	3.2 ± 1.4	0.7
K^+ intake (mmol/day)	3.3 ± 0.8	3.4 ± 1.1	0.5
IV maintenance (mL · kg^{-1} · day^{-1})	62.1 ± 12.8	65.6 ± 15.7	0.8
IV fluid replacement (mL · kg^{-1} · day^{-1})	20.6 ± 3.8	51.8 ± 14.4	0.001
Chest tube output (mL · kg^{-1} · day^{-1})	6.2 ± 4.9	8.4 ± 5.3	0.6
Net fluid balance (mL · kg^{-1} · day^{-1})	+15.7 ± 4.8	+28.9 ± 9.0	0.04

[a] Data are shown as mean ± standard deviation.

IV = intravenous; UO = urinary output.

Table 4. Hemodynamic Data

Variable	Continuous (n = 11)	Intermittent (n = 15)	*p* Value
HR (beats/min)	144.9 ± 11.7[a]	158.9 ± 14.8	0.016
CVP (mm Hg)	10.0 ± 1.4	9.9 ± 4.5	0.9
Mean BP (mm Hg)	59.6 ± 8.9	55.6 ± 5.1	0.1
Mean PAP (mm Hg)	26.9 ± 2.6	22.9 ± 5.6	0.2
Mean MVO_2 (%)	63.1 ± 18.3	60.5 ± 17.5	0.1
HR variance	88.4 ± 79.8	128.3 ± 82.7	0.09
CVP variance	2.8 ± 1.9	4.1 ± 3.7	0.07
BP variance	32.3 ± 27.6	45.7 ± 20.4	0.2
PAP variance	3.6 ± 1.9	4.0 ± 1.4	0.3
MVO_2 variance	63.9 ± 3.2	81.2 ± 4.1	0.06

[a] Data are shown as mean ± standard deviation.

BP = systemic blood pressure; CVP = central venous pressure; HR = heart rate; MVO_2 = mixed venous oxygen saturation; PAP = pulmonary artery pressure.

nitric oxide had to be started because of unsatisfactory response to intravenous pulmonary vasodilator agents.

Diuretic Effect

The efficacy of furosemide in terms of UO was satisfactory in both patient groups, although slightly greater in group 2 patients (Table 3). However, when the urinary volume was corrected for the dose of drug administered, a significantly larger response could be demonstrated with the continuous infusion. In addition, the tendency of bolus administration to cause peaks and troughs of urinary output was confirmed by the significantly greater variance in group 2 patients. A graphic representation of the diuretic response behavior using the two different administration methods is depicted in Figure 1. Due to greater variability in response to the intermittent dose, group 2 infants required a significant larger amount of intravenous fluid replacement. This finding, in fact, was not associated with a difference in volume of postoperative hemorrhage. In addition, because the discrepancy in terms of fluid replacement needs was greater than the difference in total UO, the net fluid balance during the study interval was significantly more positive in group 2 patients. The urinary and serum electrolyte levels were comparable during the study interval, which resulted in similar need for electrolyte replacement in the two groups.

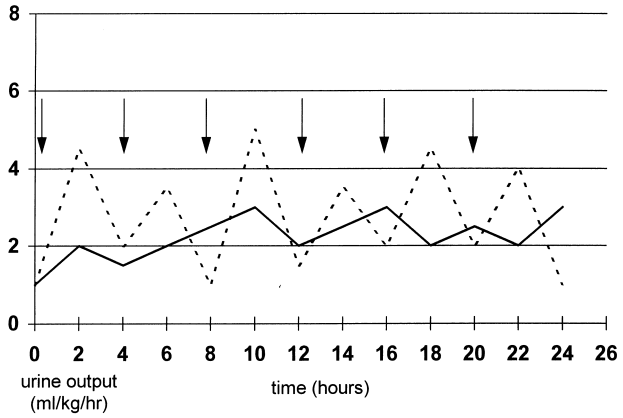

*Fig 1. Variability of urine output in infants receiving continuous furosemide infusion (*solid line*) versus infants receiving intravenous bolus administration (*broken line*). Each point in the curve represents the mean hourly urinary output at the given study time (x axis).* Arrows, *representing the time of administration of 1 mg/kg furosemide bolus in group 2 infants, have been added to highlight the relationship between dosing of the drug and peaks in urinary flow.*

Clinical and Hemodynamic Course

Given the immediate postoperative conditions, the hemodynamic profile of the infants undergoing the study was satisfactory overall (Table 4). The mean mixed venous O_2 saturation, used as an indirect index of cardiac output in patients having a biventricular repair, was acceptable for a cohort of critical infants. However, the large standard deviation for these values disclosed great variability, which was greater in group 2 patients and almost attained statistical significance. Group 2 patients showed a higher heart rate, which could be partly caused by the tendency (not significant) of these infants to be younger than group 1 patients. Nevertheless, resting heart rate had greater fluctuations in group 2 patients, as attested by a trend toward higher heart rate variance. Similarly, the variability of central venous pressure was greater in patients receiving furosemide as a bolus, although the difference did not quite reach statistical significance. These data match well the intravascular volume shifts induced by the intermittent diuretic administration (Fig 1), which were routinely recorded 30 to 60 minutes after the administration of each furosemide bolus dose. No episodes of life-threatening arrhythmias

or cardiac arrest were recorded during the study observation.

Follow-up

All of the patients who completed the study protocol were successfully weaned from mechanical ventilatory and inotropic support and eventually discharged home in satisfactory clinical conditions. The percentage of patients who required chronic furosemide therapy at discharge was comparable (73% versus 80%, group 1 versus group 2).

Comment

The hemodynamic conditions of neonates and infants with biventricular or univentricular physiology are often unstable soon after corrective or palliative cardiac surgical procedures. In addition, a total body inflammatory reaction with increased capillary permeability, generalized tissue edema, and myocardial, pulmonary, and renal dysfunction leading to decreased urinary output is a relatively common finding after procedures requiring the use of CPB in infants [1, 2]. This condition, otherwise known as postperfusion syndrome, tends to further exaggerate postoperative hemodynamic instability and to delay weaning from the ventilator because of excess tissue and lung edema.

There are a variety of possible mechanisms that contribute to renal impairment in the immediate postoperative period. These are most commonly the fluctuating circulating volume, the neuroendocrine response to the operation (increase in serum levels of catecholamine, renin/angiotensin, and antidiuretic hormone), and low cardiac output after weaning from bypass. In addition, preoperative renal dysfunction, inadequate perfusion during cardiopulmonary bypass, hemolysis, and use of nephrotoxic drugs may occasionally play a role. As a consequence, although the use of loop diuretics is generally less effective and avoided in the immediate postoperative period, in that it is thought to beget further hemodynamic instability, it would instead be indicated to reduce generalized tissue edema and hasten recovery of circulatory and respiratory insufficiency.

Loop diuretics work by blocking the active transport of chloride and sodium at the level of the thick ascending loop of Henle. The resulting natriuresis is accompanied by diuresis [8, 9]. Furosemide, a potent loop diuretic frequently employed in the postoperative management of patients undergoing cardiac surgical procedures, is commonly administered by intermittent intravenous bolus and is known to produce a prompt and vigorous diuresis that usually lasts 4 to 6 hours [8]. The response to intravenous bolus furosemide, however, is highly variable. There are a number of critically ill patients in whom the diuretic response to conventional furosemide administration may be suboptimal or even absent. These patients are generally considered "diuretic resistant" [9]. In addition, intermittent therapy may cause unpredictable fluctuations in the serum concentration of the drug, thereby exposing the patients to the risk of ototoxicity and nephrotoxicity [10, 11]. Finally, the acute changes in intravascular volume and in peripheral vascular tone associated with the bolus administration [12] may be particularly hazardous to both adult and pediatric patients in unstable hemodynamic conditions after cardiac surgical procedures.

In fact, pharmacodynamics studies have shown that the time of furosemide delivery to the receptor is a more important determinant of diuretic response than the route of administration or the total amount of drug administered [9, 13]. In particular, the diuretic effects of loop diuretics increase with increasing infusion time [9, 13]. Moving from these findings, the use of furosemide as a continuous intravenous infusion has been advocated for a variety of clinical indications [10].

Continuous Furosemide Infusion After Cardiac Operations

A recent review by Martin and Danziger [10] has identified a series of case reports and only three controlled clinical trials, two of which described the results with continuous furosemide infusion therapy in the cardiac surgical patient. In a study by Copeland and associates [5] on 18 adult patients who were hemodynamically stable after open heart operations, no significant difference was demonstrated in terms of UO. Furosemide infusion, however, offered a more constant urinary flow. Singh and colleagues [7] analyzed the relative effects of continuous versus intermittent furosemide administration in children after cardiac operations, in a prospective, randomized trial. On a series of 20 children, from infancy to preschool age, Singh and colleagues showed that a lower dose of furosemide given as continuous infusion produced the same urinary volume as a greater bolus dose, with lesser fluctuations in urinary flow and urinary losses of electrolytes. The methodology of the clinical protocol however, was unclear, as no mention was made of the timing of the study relative to the operation. In addition, only patients who were hemodynamically stable after open heart procedures were selected for the study. Thus, Singh and colleagues [7] advocated the necessity to verify these conclusions in a subset of children with greater impairment in myocardial function and higher inotropic requirement. Thus, we undertook the current study to look at the efficacy and safety of furosemide administration in neonates and young infants ($<$6 months) who are hemodynamically unstable at an early time after open heart operations.

Diuretic Effect of Furosemide Infusion in Infants

The results of our work demonstrate that commonly used doses of furosemide given both as intermittent intravenous bolus or as continuous infusion are associated with a satisfactory UO in young infants who are oliguric and hemodynamically unstable because of myocardial dysfunction, pulmonary hypertension, or both. Similar to other previous work [5, 7], we elected to use a small loading dose of furosemide before starting the continuous infusion. It has been shown that by rapidly increasing the renal tubular concentration of the drug, diuresis

will be prompt [9]. Accordingly, an appreciable diuretic response was uniformly present within 1 hour of initiation of the study in all infants randomized to the infusion regimen (Fig 1). The total UO was superior using the intermittent furosemide bolus regimen. However, this result was achieved using a significantly larger cumulative dose of drug. Indeed, correction of the urinary volume for the dose of furosemide administered revealed a significantly greater response to continuous infusion, with lesser fluctuations in hourly flow (see Table 3; Fig 1). These results are comparable with those found by Singh and associates [7] in a cohort of older children (mean age between 2 and 3 years), who were hemodynamically stable after cardiac operations and are adequately explained by the pharmacodynamic properties of furosemide [8, 9, 13]. The needs for replacement of fluids were also greater in infants receiving furosemide bolus administration. As maintenance fluid infusion and chest tube output were comparable, it is reasonable to assume this difference is a consequence of diuretic therapy and results from the larger fluctuations in UO with intermittent administration of furosemide (see Fig 1). Because of the large difference in fluid replacement requirements, the average net fluid balance after 24 hours of observations was significantly more positive in infants receiving furosemide as a bolus (see Table 3). It is, thus, noteworthy that the ultimate ability of an intermittent administration of furosemide to achieve a negative fluid balance in infants early after open heart operations may be indirectly compromised by the larger shifts in intravascular volume, as occurred in our patients.

The need for electrolyte replacement was comparable in the two patient groups. These findings agree with data reported by Singh and coworkers [7], who reported equivalent needs for electrolyte replacements, despite higher urinary loss of sodium and chloride.

Hemodynamic Effects of Furosemide Infusion in Infants

Analysis of the clinical and hemodynamic profile of infants undergoing the study showed that furosemide can be safely administered as early as 6 hours after discontinuation of CPB even in young infants with circulatory instability. As no acute cardiovascular complications occurred in relation to furosemide therapy, both intermittent bolus and continuous infusion administration proved to be adequately tolerated in this subset of patients. A tendency toward greater variability of hemodynamic parameters was found in children receiving furosemide as bolus, as attested by larger variability in heart rate, central venous pressure, and mixed venous O_2 saturation. This trend agrees well with the fluctuations in urinary flow associated with intermittent therapy demonstrated by previous studies [7]. Possible explanations for this effect are the sudden decrease in circulating plasma volume or neurohumoral vasoconstriction [11]. No evidence of adverse effects on the kidney or cardiac rhythm were observed during the clinical trial. Accordingly, instances of nephrotoxicity and supraventricular tachyarrhythmias have only been reported with prolonged use [10] or high dose (0.75 to 1 $mg \cdot kg^{-1} \cdot h^{-1}$) continuous infusion [12].

Limitations of the Study

There are at least two limitations of the present work. First, the study analyzed neither the overall impact of induction of early diuresis in neonates and young infants undergoing open heart procedures in terms of control of postperfusion syndrome, and thus of reduced need for ventilatory and inotropic support, nor the relative advantages of one mode of administration over the other. Even though the impact of early diuretic therapy cannot be analyzed in terms of avoidance of renal replacement therapy, it is noteworthy that none of these very sick infants needed to be placed on peritoneal dialysis or hemofiltration during or after the study period. Indeed, the number of clinical variables was too large and the patient population too small for meaningful assessment of the clinical benefits of such management strategy. However, we are convinced that demonstration of the efficacy and safety of loop diuretic administration in sick infants represents a necessary starting point for any prospective, randomized trials that will try to ascertain the benefits of early induction of diuresis to treat postoperative renal dysfunction and generalized fluid retention.

Second, the current protocol exposed the infants to two different starting doses of furosemide, making inferences on the diuretic efficacy of one mode of administration over the other somewhat difficult. Consequently, the possibility that the results may be related to a dose-effect relationship cannot be excluded. However, as previously stated, the current study had to meet certain ethical requirements, including the need to guarantee at least adequate postoperative diuresis to both groups of infants. Thus, the protocol was asked to respect the commonly prescribed doses of furosemide when given as continuous infusion or bolus. In addition, meaningful comparison with the only other prospective, randomized trial in the pediatric age group required similar study design [7].

Conclusions

In conclusion, both continuous infusion and intermittent intravenous bolus of furosemide, at the commonly prescribed doses, can be safely administered to neonates and infants with circulatory instability soon after open heart operations. Because of the ability to enhance a more predictable and constant urine flow, lower doses of continuous furosemide infusion may ultimately attain greater control of fluid overload with less hemodynamic instability. This method of administration appears more advantageous in the critically ill infant.

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