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RESEARCH

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Furosemide continuous infusion versus repeated injection in the management of acute decompensated heart failure in infants with left to right shunt: a randomized trial

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Abstract

Background Furosemide is the foremost drug used in the management of acute decompensated heart failure (ADHF). By tradition, it was administered as repeated intravenous boluses but fluctuations in intravascular volume and blood pressure were noticed in addition to the possibility of toxicity. Hence, continuous intravenous infusion was thought of as an alternative route of administration. In searching the literature, all previously published data concerning the pediatric age group was for infants and children following cardiac surgery. This study aims to compare the efficacy and safety of furosemide repeated injection versus continuous infusion during the management of ADHF in infants with left to right shunt.

Methods A prospective parallel-design randomized study was conducted on 54 infants with ADHF, Ross class IV, secondary to left to right shunt. Twenty-seven infants received repeated injections of furosemide and 27 infants had furosemide continuous infusion. Patients were followed clinically for weight, urine output, hours required for resolution of failure symptoms, serum creatinine, sodium and potassium, and length of hospital stay.

Results Non-significant differences were observed between both groups regarding preadmission oral furosemide dose and serum creatinine level. A lower daily dose of furosemide was observed in the continuous infusion arm (3.5 ± 0.6 vs 4.7 ± 1.0, $p = 0.001$) with less fluctuation in urine output and significantly fewer hours required for resolution of failure symptoms (42.1 ± 9 vs 56 ± 18.5, $p = 0.001$). At the end of furosemide infusion, serum creatinine was significantly higher in the continuous infusion group (0.39 ± 0.06 vs 0.34 ± 0.1, $p = 0.030$). However, before hospital discharge, non-significant differences were noticed (0.32 ± 0.05 vs 0.33 ± 0.06, $p = 0.584$). Non-significant differences between both groups regarding serum sodium and potassium levels at the end of furosemide injection were detected ($p = 0.289$, 0.890, respectively).

Conclusion Continuous infusion of furosemide can be safely administered to infants with ADHF, Ross class IV, secondary to left to right shunt with clinical gradual alleviation of fluid overload symptoms and less hemodynamic instability than repeated injections.

Trial registration The study was approved by the Mansoura Faculty of Medicine institutional research board (MS/16.02.41) on August 3rd, 2016.

Keywords Furosemide, Heart failure, Infant, Intravenous infusion

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What is known?

Furosemide is the foremost drug used in the management of acute decompensated heart failure (ADHF). In post-operative cardiac infants, continuous intravenous infusion was searched as an alternative route of administration to intravenous boluses with conflicting results. No previous studies investigated these routes in non-surgical conditions.

What does this subject add?

- Continuous furosemide intravenous infusion in acute decompensated heart failure, Ross class IV, in infants with left to right shunt may attain greater relief of fluid overload with fewer hours required for resolution of heart failure symptoms with less hemodynamic instability and less fluctuation in UOP when compared with repeated injection.
- Transient increase in serum creatinine may occur at the end of continuous furosemide infusion but returns to normal after that.

Background

Heart failure is defined as the inability of the heart to pump blood as required to meet the metabolic needs of the body resulting in systemic and/or pulmonary congestion [1, 2]. There are numerous causes of heart failure in infants; one of the most common causes is congenital heart disease with left to right shunt secondary to septal defects or patent ductus arteriosus [3]. The severity of heart failure in infants is determined by a modified Ross classification [4, 5] that grades into four classes.

The use of intravenous loop diuretics, furosemide, is a cornerstone therapy for acutely decompensated heart failure (ADHF) [6]. Major implications have been highlighted regarding the benefits and hazards of loop diuretics, particularly the route of administration and doses [7]. Furosemide is commonly used in repeated doses intravenously for ADHF, but this can cause rapid fluid shifts with marked fluctuations in intravascular volume; besides, high peak serum levels may reach toxicity [8]. Moreover, administering multiple large doses of intravenous furosemide may cause diuretic tolerance secondary to compensatory renal sodium retention that even may persist after the drug effect has abated [9]. Additionally, unfavorable neuroendocrine activation, deterioration of renal function, hypokalemia, and hyponatremia are common complications with high doses of loop diuretics [10]. Furthermore, observational studies from the acute decompensated heart failure national registry demonstrated that higher cumulative doses of loop diuretics had been associated with a higher risk of mortality, more side effects, and prolonged hospital stay [11].

Because of the side effects of intermittent high doses of furosemide, researchers investigated the effect of lower doses [12], giving subcutaneous furosemide to manage patients with ADHF at home [13] or to give through continuous infusion [14, 15].

The continuous intravenous infusion (CIVI) would encourage profuse diuresis thus decreasing congestion in systemic and pulmonary circulation without sudden blood pressure reduction [16]. Additionally, continuous infusion could provide a more constant delivery of furosemide into the tubule, potentially reducing diuretic tolerance [17]. On the other hand, despite these advantages, some authors claim that CIVI has unfavorable effects in the form of sustained neuroendocrine activation, worsening renal function, and electrolyte imbalance [16]. Several meta-analysis reviews searched the effects of furosemide CIVI versus repeated boluses in acute decompensated heart failure in adults, but have reported conflicting results [18–20]. While in the pediatric age group, CIVI was studied in post-cardiac surgery [21–24]. To our knowledge, all previous studies addressed furosemide continuous infusion in acute decompensated heart failure in the pediatric age group were for post-operative infants and children following cardiac surgery and none searched for non-surgical conditions. Therefore, this study aimed to identify the efficacy and safety of continuous intravenous infusion of furosemide versus repeated intravenous bolus administration among infants with heart failure secondary to congenital heart diseases with left to right shunt.

Methods

Study locality and duration

The prospective parallel-design randomized open-label study included 54 infants with acute heart failure secondary to congenital heart defects with left to right shunt admitted to Pediatric Cardiology and Pediatric Intensive Care Units of Mansoura University Children's Hospital, Mansoura, Egypt. The work was conducted between October 2017 and January 2021 after Mansoura Faculty of Medicine's institutional research board approval. After accepting to participate in the study, fully informed consent was signed by the parents/legal guardians of patients, and data confidentiality was considered.

Study participants

Fifty-four infants with left to right shunt, aged more than one month and less than 1 year, presented with heart failure class IV according to modified Ross classification were enrolled. Modified Ross classification class

IV incorporates the presence of tachypnea, tachycardia, hepatomegaly, diaphoresis, and signs of respiratory distress as retraction and dyspnea that necessitates the use of intravenous medications, circulatory support, and/or mechanical ventilation [4, 5].

Infants were excluded if they needed more than 6 mg/kg/day furosemide either as intermittent boluses or continuous infusion, mechanically ventilated infants, infants with chromosomal abnormalities, chronic renal impairment, heart failure precipitated by anemia or associated with infective endocarditis or sepsis. Infants who received more than one bolus of IV furosemide before randomization and infants with cardiogenic shock were also excluded.

Study design

The eligible infants were randomly assigned into two groups using the closed sealed opaque envelops; the furosemide repeated injection group involved 27 infants, who received repeated boluses of intravenous furosemide (1–2 mg/kg/dose every 8 h) and the furosemide continuous infusion group that included 27 infants, received continuous intravenous furosemide infusion (total daily dose 3–6 mg/kg).

In the repeated furosemide boluses group, furosemide was started at a dose of 1 mg/kg/dose every 8 h, the attending physician titrated the dose by 0.25 mg/kg/dose according to the patient´s response till 2 mg/kg/dose (maximum total daily dose 6 mg/kg/day). For the continuous furosemide infusion group, all infants received a bolus dose of IV furosemide (1 mg/kg) once by the physician in the Emergency room before starting CIVI therapy, the starting dose of furosemide was 0.125 mg/kg/h IVI and the attending physician could increase by 0.025 mg/kg/h till a maximum of 0.25 mg/kg/h (maximum total daily dose 6 mg/kg/day). During the administration of CIVI of furosemide, the IV line was covered by aluminum foil to generate light protection during IVI as furosemide is light-sensitive. The attending physician decided to stop IV furosemide when no signs of peripheral edema (eye, face, or sacral), the patient's heart rate and respiratory rate became normal for his/her age, started oral intake, and no dyspnea on feeding. Patients could leave the study at any time if the attending physician observed that the patient had unstable hemodynamics, shock, deterioration of congestive symptoms, worsening of renal function, or marked electrolyte disturbances. In the current study, none of the involved patients expressed any of the previous criteria and all patients completed the study.

During the course of the study and according to the clinical state of each infant, supplemental oxygen guided by pulse oximetry could be ordered by the treating physician. The preadmission cardiac medications such as captopril and/or oral digoxin were initially maintained at the same dose then the dose was adjusted by the treating physician according to the patient's condition. IV fluid was restricted to 65–70% of the maintenance daily fluid requirement according to the hospital policy then the amount was adjusted by the treating physician according to the patient´s condition. The treating physician gave boluses of fluid (10 ml/kg once) to two patients in the furosemide repeated injection group because of hypotension and prolonged capillary refill time that occurred after the furosemide bolus while in the continuous furosemide infusion group, no fluid boluses were administered.

Data were collected from all patients including age, gender, anthropometric measures (weight and height), underlying cardiac lesions, echocardiographic findings, precipitating factors of heart failure, and heart failure symptoms; besides, preadmission medications (doses and duration) were registered. Daily IV fluid intake was recorded. Patients were monitored clinically for heart rate, respiratory rate, blood pressure, O2 saturation and urine output (UOP) (ml/kg/h) for at least 49 h at certain intervals that represented the timing of furosemide bolus and 1 h after (0 (on admission), 1, 8, 9, 16, 17, 24, 25, 32, 33, 40, 41, 48, 49) as peak action of furosemide is 30 min after injection [25]. All patients eligible for the study were catheterized to ensure accurate documentation of hourly UOP. Body weight and laboratory investigations (serum sodium, potassium, and creatinine) were measured every 24 h. Body weight was measured daily to all studied patients at 9 am (before the diuretic bolus dose in the furosemide repeated injection group).

Study outcomes

The primary outcome measure was the hours required for the resolution of failure symptoms in the scope of modified Ross classification that indicates improvement of tachypnea, tachycardia, diaphoresis, normal breathing pattern and perfusion, and no hepatomegaly with tolerated oral feeding. Secondary outcome measures encompassed serum creatinine level, changes in electrolytes (serum sodium and potassium), total daily doses of IV furosemide in both groups, length of hospital stay, and in-hospital mortality. Patients were followed after hospital discharge for thirty days for rehospitalization rate with ADHF and mortality. We gave the enrolled patients appointments in the cardiology outpatient clinic at 2 weeks and 4 weeks after discharge to be examined for any signs of congestion while for those who did not come, the treating physician called them to know their clinical states.

Study power

Sample size calculation was based on the difference in the time elapsed for resolution of failure symptoms (hours) between the furosemide continuous infusion group versus the repeated injection group in the management of acute decompensated heart failure in infants with left to right shunt retrieved after a pilot study carried out on 10 patients in each group (then excluded from analysis). Using G*power version 3.0.10 to calculate sample size based *t* test = 2.00, 2-tailed, α error = 0.05 and power = 90.0% with an effect size (0.905), mean ± standard deviation (SD) of time elapsed to start oral feeding (40 ± 10 and 50 ± 12), the total calculated sample size will be 54 participants (27 in each group).

Statistical analysis

Data were analyzed with SPSS® Statistics (SPSS, IBM Company, Chicago, IL, USA) version 23. The normality of data was first tested with the Shapiro–Wilk test. Continuous variables were presented as mean ± SD for parametric data and were compared with Student's *t* test. Qualitative data were described using frequency and percent. Association between categorical variables was tested using chi-square/Fisher's exact tests. The *P* value to reject the null hypothesis and consider statistical significance is < 0.05.

Results

Between October 2017 and January 2021, a total of 61 infants with ADHF secondary to congenital heart disease with left to right shunt were eligible for the study. Of those, 54 infants were allocated to randomization either in the furosemide repeated injection group ($n = 27$) or continuous infusion group ($n = 27$) and 7 infants were excluded due to a variety of causes (Fig. 1).

Baseline characteristics, clinical data, and laboratory data at the time of allocation were non-significantly different between the studied groups as summarized in Table 1. For demographic characteristics, patients' age, gender, and anthropometric measures did not

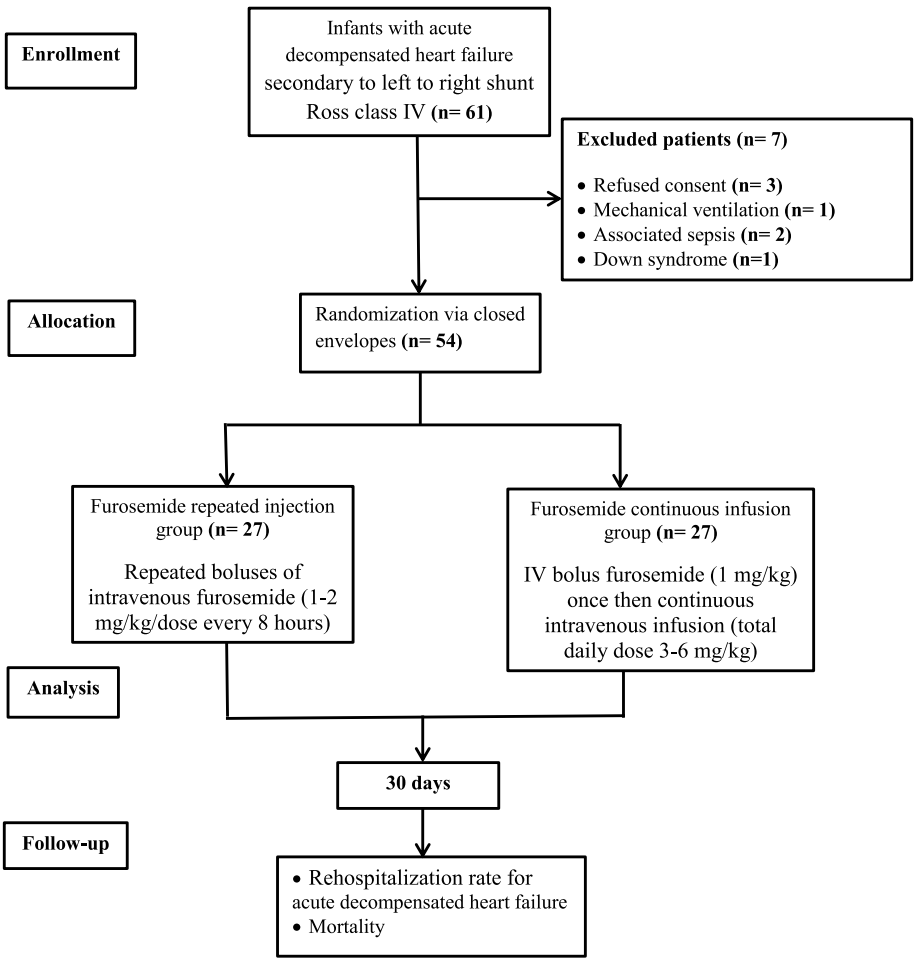

Fig. 1 CONSORT flowchart of the study population

Table 1 Demographic characteristics, echocardiographic, clinical, and laboratory data of the study groups before the start of the furosemide injection

	Furosemide repeated injection ($n=27$)	Furosemide continuous infusion ($n=27$)	*P* value
Gender[a]			
Male/female	16/11	15-Dec	0.414
Age[b] (month)	6.11 ± 3.18	6.06 ± 3.19	0.954
Weight[b] (kg)	5.35 ± 1.52	5.24 ± 1.52	0.789
Height[b] (cm)	59.26 ± 6.77	60.70 ± 6.12	0.415
Underlying cardiac lesions[a]			
VSD	6 (22.2)	9 (33.3)	0.18
PDA	5 (18.5)	2 (7.4)	
VSD + ASD	9 (33.3)	12 (44.4)	
VSD + PDA	0	2 (7.4)	
ASD + PDA	5 (18.5)	2 (7.4)	
VSD + ASD + PDA	2 (7.4)	0	
Echocardiography findings[a]			
Left ventricular ejection fraction	47.67 ± 5.87	46.64 ± 7.32	0.578
Size of the lesions			
VSD (mm)	7.31 ± 2.09	8.19 ± 2.96	0.37
ASD (mm)	5.44 ± 3.14	4.54 ± 2.40	0.403
PDA (mm)	4.17 ± 1.47	5 ± 0.82	0.304
Precipitating factors of ADHF[a]			
Acute bronchiolitis	10 (37)	10 (37)	0.775
Pneumonia	10 (37)	9 (33.3)	
Gastroenteritis	7 (25.9)	6 (22.2)	
Incompliance to therapy	0	2 (7.2)	
Preadmission oral furosemide [b]			
Number of patients	$n=22$	$n=24$	
Dose (mg/kg/day)	1.3 ± 0.25	1.38 ± 0.34	0.374
Clinical data[b]			
HR (beat/min)	170.7 ± 6.2	171.6 ± 5.3	0.557
RR (/min)	71.6 ± 5.9	73.4 ± 3.4	0.175
SBP (mmHg)	109.2 ± 7.6	111.9 ± 6.4	0.158
DBP (mmHg)	71.7 ± 3.7	70.1 ± 4.2	0.145
SpO2 (%)	78.2 ± 3.6	77. 7 ± 4.4	0.692
Laboratory data[b]			
Serum sodium (mmol/l)	137.9 ± 2.3	138.3 ± 2.6	0.541
Serum potassium (mmol/l)	3.67 ± 0.41	3.71 ± 0.47	0.758
Serum creatinine (mg/dl)	0.57 ± 0.12	0.60 ± 0.12	0.432

VSD Ventricular septal defect, *ASD* Atrial septal defect, *PDA* Patent ductus arteriosus, *ADHF* Acute decompensated heart failure, *UOP* Urine output, *HR* Heart rate, *RR* respiratory rate, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *SpO2* Oxygen saturation by pulse oximetry, */min* per minute

Data expressed as number (percent)/ratio [a] or mean ± SD [b] and analyzed by chi-square/Fisher´s exact test[a] and Student's *t* test [b]; respectively

significantly differ between the study groups. The underlying congenital heart diseases with left to right shunt in the studied infants were ventricular septal defect, atrial septal defect, patent ductus arteriosus, or a combination of more than one lesion with non-significant differences between the study groups ($P=0.180$). In the furosemide repeated injection group, 10 patients had pneumonia and 10 had acute bronchiolitis which were comparable to the furosemide continuous infusion group in which 9 patients suffered from acute pneumonia and 10 had acute bronchiolitis. This infection could explain the low oxygen saturation. Moreover,

congestive heart failure with pulmonary congestion could develop a ventilation-perfusion mismatch that would be accompanied by low oxygen saturation.

Table 2 demonstrates the study discussion points which are the detected changes after 24 h of therapy with IV furosemide (values of data measured at 24 h—values of data measured on hospital admission) and the changes after 48 h of therapy (data measured at 48 h—data measured on admission). For changes after the 24 h of furosemide therapy, significantly higher weight loss (−0.33 ± 0.05 vs −0.27 ± 0.05; $P=0.001$) and higher UOP (3.3 ± 1.4 vs 2.6 ± 1.0; $p=0.037$) in furosemide continuous infusion group were observed and these changes were impacted on HR and RR. Likewise, changes after the 48 h of furosemide therapy show significantly higher weight loss in the furosemide continuous infusion group (−0.59 ± 0.11 vs −0.49 ± 0.07, $P=0.001$) with higher UOP (2.3 ± 1.3 vs 1.2 ± 0.3; $P=0.001$) were noticed. For more analysis, UOP was measured in both groups at certain intervals that represented the timing of furosemide bolus (in the furosemide repeated injection group) and 1 h after (0 (on admission), 1, 8, 9, 16, 17, 24, 25, 32, 33, 40, 41, 48, and 49). It was observed that UOP in the furosemide repeated injection group showed up and down levels indicating fluctuation in UOP level while in the furosemide continuous infusion group, there were smoother changes in UOP (Fig. 2).

In Table 3, a significantly lower daily dose of furosemide was observed in the furosemide continuous infusion group (3.5 ± 0.6 vs 4.7 ± 1; $P=0.001$) with fewer hours required for resolution of failure symptoms (42.1 ± 9 vs 56 ± 18.5; $P=0.001$). Non-significant differences between both groups regarding length of hospital stay were detected. For serum creatinine, at the end of furosemide injection, significantly higher levels were noticed in the furosemide continuous infusion group despite being within the normal range in both study groups ($p=0.030$); however, at hospital discharge, non-significant differences were observed between the studied groups ($p=0.584$). Concerning the electrolyte levels, serum sodium and potassium levels did not significantly differ between the studied groups ($P=0.289$, 0.890; respectively). During the 30 days' follow-up period, non-significant differences between both groups as to rehospitalization rate for ADHF were documented with no detected mortality among the studied patients.

Discussion

Furosemide injection is the mainstay for the relief of pulmonary and systemic congestion in infants with ADHF [6]. A high dose of furosemide repeated injection was associated with increased morbidity and mortality [11]; hence, other routes of administration were researched. In searching in the previous articles, conflicting results of the studies comparing both modalities of furosemide administration in adults were noted with multiple meta-analyses performed. Limited data are available from pediatric research, all following cardiac surgery. To the best of our knowledge, the comparative study of different routes of furosemide administration in the pediatric age group following non-surgical conditions has never been addressed before in original articles. In the current work,

Table 2 The clinical and laboratory data of the study groups after the start of the furosemide injection

	Changes after 24-h therapy (24-h data–admission data)			Changes after 48-h therapy (48 h data–admission data)		
	Furosemide repeated injection ($n=27$)	Furosemide continuous infusion ($n=27$)	*P* value	Furosemide repeated injection ($n=27$)	Furosemide continuous infusion ($n=27$)	*P* value
ΔWeight (kg)	−0.27 ± 0.05	−0.33 ± 0.05	0.001	−0.49 ± 0.07	−0.59 ± 0.11	0.001
ΔUOP (ml/kg/h)	2.6 ± 1.0	3.3 ± 1.4	0.037	1.2 ± 0.3	2.3 ± 1.3	0.001
ΔHR (beat/min)	−18.5 ± 4.4	−23.3 ± 6.3	0.002	−27 ± 3.7	−28 ± 4	0.324
ΔRR (/min)	−15.1 ± 2.6	−18.8 ± 2.9	0.001	−20 ± 3	−24.5 ± 3.3	0.001
ΔSBP (mmHg)	−27. 8 ± 6.8	−26. 6 ± 9.6	0.613	−35 ± 6.5	−33 ± 7.7	0.214
ΔDBP (mmHg)	−20.6 ± 5.5	−23.3 ± 7.6	0.138	−28 ± 5.5	−27.7 ± 6.9	0.897
ΔSpO2 (%)	12.6 ± 3.4	12.7 ± 4.4	0.945	16.2 ± 3.8	16.1 ± 4.3	0.893
Δ Serum sodium (mmol/l)	3.1 ± 1	2.7 ± 0.9	0.111	3.9 ± 1.6	4.1 ± 1.5	0.662
ΔSerum potassium (mmol/l)	−0.31 ± 0.08	−0.37 ± 0.2	0.185	−0.51 ± 0.33	−0.56 ± 0.47	0.816
ΔSerum creatinine (mg/dl)	−0.12 ± 0.05	−0.11 ± 0.06	0.627	−0.23 ± 0.06	−0.20 ± 0.09	0.248

UOP Urine output, *HR* Heart rate, *RR* Respiratory rate, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *SpO2* Oxygen saturation by pulse oximetry, */min* per minute

Data expressed as mean ± SD and analyzed by Student's *t* test

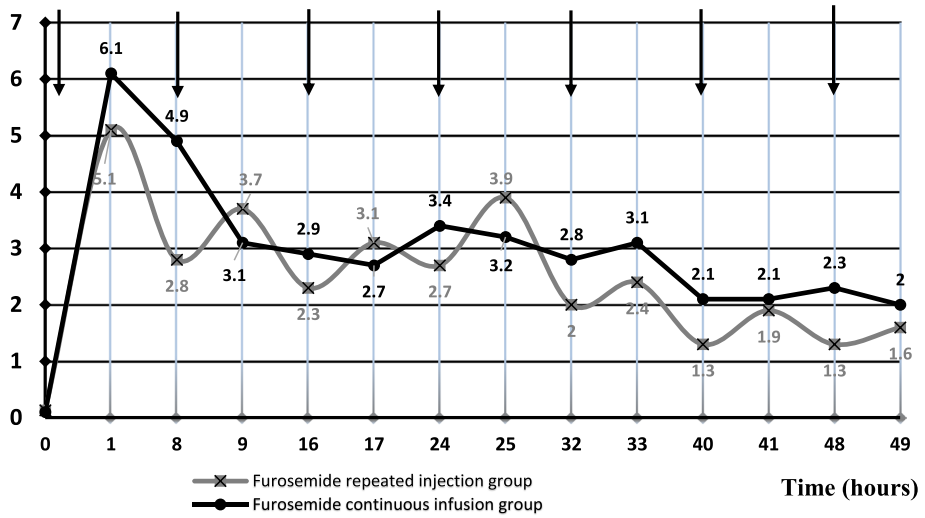

Fig. 2 Changes in urine output over 49 h in infants with acute decompensated heart failure secondary to congenital heart diseases with left to right shunt. The arrows refer to the timing of giving furosemide in repeated injection group

Table 3 Clinical and laboratory outcome measures of the studied patients' groups

	Furosemide repeated injection (*n* = 27)	Furosemide continuous infusion (*n* = 27)	*P* value
Time elapsed for resolution of failure symptoms[b] (h)	56 ± 18.5	42.1 ± 9.0	0.001
Furosemide dose in the first 2 days[b] (mg/kg/day)	4.7 ± 1.0	3.5 ± 0.6	0.001
Serum sodium at the end of furosemide injection[b] (mmol/l)	141.8 ± 1.5	142.4 ± 2.5	0.289
Serum potassium at the end of furosemide injection[b] (mmol/l)	3.1 ± 0.2	3.1 ± 0.4	0.890
Serum creatinine at the end of furosemide injection[b] (mg/dl)	0.34 ± 0.1	0.39 ± 0.06	0.030
Serum creatinine at hospital discharge[b] (mg/dl)	0.33 ± 0.06	0.32 ± 0.05	0.584
Length of hospital stay[b] (days)	12.2 ± 3.0	12.4 ± 3.2	0.724
30 days rehospitalization rate for ADHF[a]	9 (33.3%)	7 (25.9%)	0.766
In-hospital mortality[a]	0	0	
30 days mortality[a]	0	0	

ADHF acute decompensated heart failure

Data expressed as number (percent) [a] or mean ± SD[b] and analyzed by Fisher's exact test[a] and Student's *t* test[b], respectively

furosemide repeated injection and continuous IV infusion were compared in critically ill infants with ADHF secondary to left to right shunt. Furosemide continuous infusion was associated with significantly more urine output, less daily dose of IV furosemide, and less elapsed time for resolution of congestive symptoms.

In the present study, when comparing the changes in the weight and UOP at 24 and 48 h after administration of furosemide injection, significantly higher weight loss and higher UOP in the continuous furosemide infusion group. Moreover, continuous infusion allows more smooth constant flow in UOP (indicating constant and sustained diuresis) when compared with intermittent boluses that cause a sharp increase (following furosemide injection) and then decreases (before the dose of the next bolus injection) in UOP, indicating a sharp fluctuation in the diuretic effect of furosemide, which gave an impression on serum furosemide concentration. These results were in concordance with multiple previous studies as reviewed. In a study conducted by Luciani et al. [22] to assess and compare the safety and efficacy of continuous versus intermittent IV furosemide post-open heart surgery, they conducted a prospective, randomized clinical trial in 26 infants aged younger than 6 months. They noticed slightly greater urinary volume in the intermittent injection group. However, when it was corrected

for the dose of administered furosemide, a significantly larger response could be demonstrated with the continuous infusion. In addition, the continuous furosemide infusion caused lesser fluctuation in UOP with less fluid replacement therapy needed. Also, Llorens et al., [26] and Singh and coworkers [21] reported the efficient diuresis in continuous furosemide infused patients. Moreover, Zheng and co-authors [27] compared the effect of continuous furosemide infusion versus repeated injection in the resolution of congestive symptoms in adult patients with acute decompensated heart failure associated with moderate renal impairment. After 72-h therapy, they observed higher UOP, more weight loss, and shorter length of stay in the continuous infusion category. This could be explained by a continuous infusion of furosemide will produce consistent plasma concentration and may have a more consistent diuretic effect, producing a greater total urinary volume than following a repeated bolus injection.

In the other hand, when reviewing studies comparing the effectiveness of continuous IV furosemide infusion versus intermittent injection in patients with acute decompensated heart failure, an adult prospective, randomized study by Thomson et al. [28] found that, despite higher total UOP in continuous furosemide infusion group, the mean weight loss was not significantly different between both groups. Furthermore, another study performed by Klinge and co-authors [23] included 46 post-open heart surgery pediatric patients, who were randomly assigned to continuous furosemide IV infusion or intermittent injection and showed significantly higher hourly UOP with intermittent furosemide injection when compared with continuous infusion. Moreover, they observed that a lower dose of furosemide in the intermittent injection group produced the same 24-h urine volume as continuous infusion. This later study was performed on postoperative hemodynamically stable cardiac patients with less furosemide dose requirement. However, In 2001, Van der Vorst et al. [24] conducted a study on postoperative hemodynamically unstable cardiac patients. They undertook a prospective trial in [12] patients less than 8 months of age, all patients received continuous IV furosemide infusion over 3 days. The furosemide dose was gradually changed hour by hour guided by the observed effect on UOP. They observed the beneficial effect of continuous furosemide infusion in hemodynamically unstable children post-cardiac surgery. Moreover, Singh and colleagues [21] analyzed 20 postoperative cardiac children, younger than 6 years, for the efficacy of continuous infusion versus intermittent furosemide injection in a prospective, randomized trial. The analysis showed that a smaller dose of furosemide continuous infusion produced the same total UOP as a higher bolus dose, with lesser fluctuation in urinary volume and less variability in electrolytes.

In the present study, in analyzing data from continuous furosemide infusion and repeated injection groups, non-significant differences in serum sodium and serum potassium were observed after 24-h and 48-h therapy and at the end of furosemide infusion. These data were in concordance with Shah and coworkers [15] who followed patients with acute decompensated heart failure for 48 h of continuous furosemide infusion (30 patients) and an intermittent injection every 12 h (30 patients) and observed non-significant differences in serum sodium and potassium levels. The same results were observed by Zheng et al. 2021 [27] as they studied patients with acute decompensated heart failure associated with chronic renal impairment and observed non-significant differences in the frequency of electrolyte disturbances despite increased total urinary sodium excretion. On the contrary, significant hypokalemia was detected in the continuous furosemide infusion group by Llorens et al. [26] while serum sodium did not significantly differ. Yet, with a deeper look at the study, the authors followed patients for 24 h only and did not comment on potassium supply. However, Allen et al. [14] reported that side effects (i.e., hypokalemia) may potentially be improved in the continuous infusion strategy. This could be explained as furosemide performing its action through its diuretic mechanism or direct blocking of sodium chloride uptake and up-regulation of renin gene expression hence, stimulation of renin release. However, in persistent volume expansion in patients with chronic congestive heart failure, natriuresis becomes lower even with volume overload [29].

In the present study, non-significant changes in serum creatinine levels were observed after 24 h and 48 h of therapy between continuous furosemide infusion and repeated injection groups; however, at the end of furosemide infusion, serum creatinine was significantly higher in the continuous infusion group. With a deeper look, we observed that creatinine level was within the normal range in both groups at the end of furosemide injection, and with analysis of its level before patients' hospital discharge, a non-significant difference was observed. With searching in the literature, we found this observation of transient affection of renal function after furosemide infusion was mentioned by Felker et al. [30] as there was also a slightly higher change in serum creatinine level from baseline after 72 h of continuous furosemide infusion (mean change in creatinine level, 0.07 ± 0.3 mg/dl in continuous furosemide infusion versus 0.05 ± 0.3 mg/dL with repeated injection) but this difference did reach any

statistical significance ($P=0.45$). Another randomized clinical trial performed by Palazzuoli et al. [16] studied 82 adult patients with acute decompensated heart failure (43 patients received continuous infusion and 39 repeated injections of furosemide). At discharge from the hospital, the mean change in serum creatinine was significantly higher in the continuous infusion category ($+0.8 \pm 0.4$ versus -0.8 ± 0.3 mg/dl $P<0.01$); however, the rate of acute kidney injury was comparable between both studied groups ($P=0.3$). On the other hand, other authors who studied furosemide in acute decompensated heart failure did not find significant differences in serum creatinine between continuous furosemide infusion and repeated boluses groups [14, 15, 26, 27, 31].

One of the strengths of our study is that it investigates the efficacy and safety of furosemide infusion in infants with acute decompensated heart failure secondary to medical causes while all previously published data concerning pediatric age group was for infants and children following cardiac surgery. Second, the study was designed as a two parallel-groups randomized trial and this offers an advantage over the cross-over design as no intervening washout period of furosemide so the results are real values to the administered modality of injected furosemide. Third, participants in this study are all with acute decompensated heart failure secondary to left to right shunt and this allows homogeneity of the pooled estimated data. Fourth, in the present study, the dose of the injected furosemide ranged from 3 to 6 mg/kg/day in both modalities to avoid the effects of higher doses of furosemide and to ensure the efficacy and safety are related to the mode of administration not to the dose differences.

One of the limitations of the study is the small sample size accordingly, future research on a larger number of patients with high power is critically required to detect the potentially important difference in creatinine between patients on furosemide intermittent boluses and continuous infusion. Moreover, due to the observational design of the study, the stoppage of furosemide, the doses of furosemide boluses, and continuous infusion and fluid boluses were estimated by the treating physician according to the patient's clinical condition and the hospital policy.

Conclusion

Lower doses of furosemide intravenous infusion in acute decompensated heart failure, Ross class IV, in infants with left to right shunt may attain greater relief of fluid overload with fewer hours required for resolution of heart failure symptoms with less hemodynamic instability and less fluctuation in UOP when compared with repeated injection. With the view of these results, it is recommended to give furosemide continuous infusion, after a single initial bolus, in infants with acute decompensated heart failure, Ross class IV, secondary to left to right shunt and advice to add in the guidelines for management of ADHF.

Abbreviations

/min	Per minute
α	Alpha
ADHF	Acute decompensated heart failure
am	Ante Meridiem
ASD	Atrial septal defect
CIVI	Continuous intravenous infusion
DBP	Diastolic blood pressure
HR	Heart rate
IBM´s SPSS	Statistical Package for the Social Sciences
IV	Intravenous
IVI	Intravenous infusion
Kg	Kilogram
PDA	Patent ductus arteriosus
P value	Probability value
RR	Respiratory rate
SBP	Systolic blood pressure
SD	Standard deviation
SpO2	Oxygen saturation by pulse oximetry
UOP	Urine output
VSD	Ventricular septal defect

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Authors' contributions

MZ shared the research protocol, collected patients' blood samples and clinical data, and approved the final manuscript. BH shared in the research protocol, supervised the provided medical care to some patients, and approved the final manuscript. MMA participated in the formulation of the research hypothesis and plan, supervised the provided medical care to all patients, and approved the final manuscript. HE formulated the research hypothesis and protocol, data collection and interpretation, did the statistical analysis of the data, wrote the first draft, and revised and approved the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data and materials are available upon request.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Mansoura Faculty of Medicine Institutional Research Board (IRB) (MS/16.02.41). Written informed consent was obtained from parents and/or legal guardians of the study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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