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Original Article

The use of nesiritide in patients with critical cardiac disease

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Abstract *Objective:* We evaluated the use of nesiritide in children with critical CHD, pulmonary congestion, and inadequate urine output despite undergoing conventional diuretic therapy. *Design:* We conducted a retrospective analysis of 11 patients with critical CHD, comprising 18 infusions, each of which occurred during separate hospitalisations. Haemodynamic parameters were assessed, and the stage of acute kidney injury was determined before and throughout the duration of therapy using a standardised definition of acute kidney injury – The Kidney Disease: Improving Global Outcomes criteria. *Patients:* Children with critical CHD, pulmonary congestion, and inadequate urinary output despite undergoing diuretic therapy were included. *Measurements and main results:* The use of nesiritide was associated with a significant decrease in the maximum and minimum heart rate values and with a trend towards a significant decrease in maximum systolic blood pressure and maximum and minimum central venous pressures. Urine output increased but was not significant. Serum creatinine levels decreased significantly during the course of therapy (–0.26 mg/dl [–0.50, 0.0], $p = 0.02$), and the number of patients who experienced a decrease in the stage of acute kidney injury of 2 or more – where a change in the stage of acute kidney disease of 2 or more was possible, that is, baseline stage >1 – was highly significant (five of 12 patients, 42%, $p < 0.001$). *Conclusions:* Nesiritide had a favourable impact on haemodynamics, and its use was not associated with deterioration of renal function in patients with critical CHD.

Keywords: Nesiritide, CHD; single-ventricle physiology; acute kidney injury

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NESIRITIDE IS A RECOMBINANT FORM OF HUMAN B-type natriuretic peptide with diverse biological actions including inhibition of neurohormonal pathways, dieresis, and vasodilation of arterial resistance and venous capacitance vessels.[1] Nesiritide received approval from the United States Food and Drug Administration in 2001 to treat acute decompensated heart failure in adults. The endogenous biological activity of the natriuretic hormone system may be inadequate in patients with heart failure due to functional derangements in the B-type natriuretic peptide/cyclic guanosine monophosphate signalling pathway, providing the rationale for the administration of exogenous B-type natriuretic peptide.[2,3] In 2005, a meta-analysis was conducted on the use of nesiritde for acute decompensated heart failure in adults who demonstrated an association between nesiritide and worsening renal function, which led to a rapid decline in nesiritide use.[4] Recently, however, van Deursen et al[5] conducted a randomised study to evaluate the effects of nesiritide on renal function during hospitalisation for acute decompensated heart failure in adults. The frequency of worsening renal function during hospitalisation was similar in the nesiritide and placebo groups ($p = NS$).[5] Despite the fact that there are no published reports in children demonstrating an

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association between nesiritide and worsening renal function, the use of nesiritide in children also decreased significantly. Since the meta-analysis by Sackner-Bernstein et al, there have been published reports from three centres that found no worsening of renal function in children with CHD and acquired heart disease treated with nesiritide.[6–10] An important limitation of these studies, however, is that the duration of monitoring of renal function, which was 24–72 hours, was considerably shorter than the trials that comprised the meta-analysis.

We evaluated the impact of nesiritide on haemodynamics and renal function in patients with critical CHD throughout the duration of therapy by applying a standardised definition of acute kidney injury, The Kidney Disease: Improving Global Outcomes criteria, to establish the severity of acute kidney injury at baseline – before the initiation of nesiritide – and to monitor the evolution of acute kidney injury until the last day of therapy with nesiritide.[11]

Materials and methods

Study design

This was a retrospective review that included patients with critical CHD and pulmonary congestion, who despite the use of conventional diuretics received nesiritide over a 3-year period. Critical CHD for the purposes of this study was defined as patients with single-ventricle anatomy and physiology and biventricular anatomy and single-ventricle physiology. Data included patient demographics, underlying cardiovascular disease, and concomitant use of vasoactive and diuretic medications (Table 1). A vasoactive–inotropic score[12] was calculated for each nesiritide infusion. The study was exempted by the institutional review board, and the requirement for informed consent was waived.

Nesiritide dosing and indications

A protocol was established for the use of nesiritide. The protocol specified that patients with CHD, pulmonary congestion, and inadequate urine output despite loop and/or thiazide diuretic therapy were eligible for nesiritide infusion. The protocol stated that the dosing of conventional diuretics – loop and or thiazide diuretics – was to remain unchanged during infusion of nesiritide, there should be no loading dose, the starting dose and duration of the nesiritide infusion are to be at the discretion of the clinician, and the infusion was not to be initiated during the initial 96 hours following cardiac surgery. The use of other vasoactive agents was at the discretion of the clinician. The protocol also called for

Table 1. Patient demographics and medications used.

Patient number	Infusion number	Diagnosis	Age (months)	Weight (kg)	Duration of infusion (hours)	Starting dose	Maximum dose	Vasoactive agents	Diuretics
1a	1	HLHS	0.2	3.8	83	0.015	0.020	0.30 M; 4 DA	6 hours L
1b	2	HLHS	1	3.9	292	0.010	0.020	0.50 M	6 hours L
2a	3	HLHS	3.3	5.6	410	0.010	0.030	0.25 M	6 hours L
2b	4	HLHS	4.5	6.0	127	0.010	0.010	0.25 M; 0.01 E	8 hours L
2c	5	HLHS	4.6	6.0	94	0.010	0.020	0.25 M	6 hours L
2d	6	HLHS	4.7	6.0	218	0.010	0.010	0.25 M	6 hours L
3a	7	HLHS	0.3	3.2	405	0.005	0.020	0.50 M; 5 DA; 0.05 E	0.2 L
3b	8	HLHS	3.5	5.4	79	0.010	0.020	0.50 M	0.5 L
4	9	Complex SV variant	0.3	2.6	55	0.010	0.020	8 DA; 0.05 E	8 hours L
5	10	HLHS	0.4	3.6	80	0.010	0.030	0.50 M; 0.1 E	
6a	11	Truncus	0.5	1.3	127	0.010	0.020	–	12 hours L
6b	12	Truncus	0.6	1.3	76	0.010	0.020	0.30 M; 5 DA; 0.08 E	12 hours L
7a	13	HLHS	0.3	3.9	155	0.010	0.020	0.40 M; 10 DA; 0.05 E	0.2 L
7b	14	HLHS	2.7	5.7	62	0.010	0.030	0.60 M; 4 DA	6 hours L
8	15	Complex SV variant	0.2	3.6	72	0.010	0.020	0.20 M; 5 DA; 0.01 E	8 hours L
9	16	HLHS	5	4.6	162	0.010	0.030	0.40 M; 13 DA	8 hours L
10	17	Complex SV variant	0.3	3.8	492	0.010	0.030	0.10 M; 3 DA; 0.04 E	0.5 L
11	18	Complex SV variant	5	4.3	38	0.010	0.030	0.40 M; 3 DA	8 hours L

D, diuril; duration = starting and maximum doses (μg/kg/min) for nesiritide; maximum rates of infusion for M = milrinone (mg/kg/minute); E = epinephrine (μg/kg/minute); DA = dopamine (μg/kg/minute); HLHS = hypoplastic left heart syndrome; L = lasix (frequency of dosing in hours or maximum drip rate [mg/kg/hour]); SV = single ventricle; truncus = truncus arteriosus

Patient number represents each patient with each of their separate infusions (enumerated using the alphabet)

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Table 2. Kidney Disease: Improving Global Outcomes criteria for staging of acute kidney injury.

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline Or ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	<0.5 ml/kg/hour for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/hour for ⩾12 hours
3	3.0 times baseline Or Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) Or Initiation of renal replacement therapy Or, in patients <18 years, decrease in eGFR to <35 ml/min/1.73 m^2	<0.3 ml/kg/hour for ⩾24 hours OR Anuria for ⩾12 hours

eGFR = estimated glomerular filtration rate

determination of baseline, or pre-nesiritide, and daily serum creatinine levels.

Acute kidney injury stratification

Acute kidney injury was defined and staged using The Kidney Disease: Improving Global Outcomes creatinine criteria (Table 2).[11] As nesiritide is a diuretic, urine output was not used to determine The Kidney Disease: Improving Global Outcomes stage of acute kidney injury. Serum creatinine levels were measured before and daily during nesiritide infusion. The baseline stage of acute kidney injury, that is, before initiating nesiritide, and stage of acute kidney injury during the infusion were determined using the following approach: normative (median) values of serum creatinine indexed to narrow age intervals, as determined by Boer et al,[13] were used to determine the patient's stage of acute kidney injury. If the patient's creatinine level was 1.5–1.9 times the normative creatinine value, stage 1 acute kidney injury criteria were met; if the patient's creatinine level was 2.0–2.9 times the normative creatinine value, stage 2 acute kidney injury criteria were met; and if the patient's creatinine level was greater than three times the normative creatinine value, stage 3 acute kidney injury criteria were met. The same approach was used to determine the stage of acute kidney injury before the initiation of nesiritide and to determine the stage of acute kidney injury during nesiritide infusion. Changes in the stage of acute kidney injury were based on a comparison between day(s) of infusion and baseline or pre-nesiritide stage of acute kidney injury.

Haemodynamic data

The daily maximum and minimum systolic blood pressure values were obtained from either an indwelling arterial catheter or a pneumatic cuff. The daily maximum and minimum heart rates were also recorded. The daily maximum and minimum central venous pressures were obtained from an indwelling venous catheter. Daily urine output was measured using an indwelling urinary catheter. Haemodynamic data were collected for days 0 through 4.

Statistical analysis

Summary statistics are reported as medians (25th–75th percentile) or numbers (percentage [%]). We compared pre-infusion measures with measures on subsequent days using Wilcoxon's signed rank test. The threshold for establishing statistical significance was adjusted using Bonferroni's correction to account for multiple comparisons, which lowered the required p-value to 0.013 for haemodynamic parameters and urine output and to 0.008 for creatinine, and The Kidney Disease: Improving Global Outcomes stage of acute kidney injury to meet criteria for statistical significance. We tested significance for differences in The Kidney Disease: Improving Global Outcomes staging – that is, change in stage of acute kidney injury of 2 or more for all patients and in reference to baseline stage of acute kidney injury (>1 and <2) – between pre-infusion values and final day values with the binomial exact test. Strengths of association between medication exposures – vasoactive-inotropic score, maximum nesiritide dose, and duration of nesiritide treatment – and renal function – creatinine and The Kidney Disease: Improving Global Outcomes stage – were measured using the Spearman Correlation Coefficient. Analyses were performed using SAS 9.4 (SAS Institute, Incorporated, Cary, North Carolina, United States of America).

Results

Study patients

The median age and weight of patients were 0.8 months (0.3, 4.3) and 3.9 kg (3.6, 5.6), respectively. The data from 11 children with critical CHD

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Table 3. Haemodynamic changes during treatment.

Parameter	Pairs	Median (25th–75th %)	p-value
Minimum systolic blood pressure (mmHg)			
Day 1 versus pre	17	− 3 (−9, 5)	0.36
Day 2 versus pre	17	− 2 (−11, 5)	0.41
Day 3 versus pre	16	− 2 (−7, 5)	0.62
Day 4 versus pre	12	− 2 (−11, 1)	0.16
Maximum systolic blood pressure (mmHg)			
Day 1 versus pre	17	− 3 (−13, 5)	0.43
Day 2 versus pre	17	− 2 (−6, 3)	0.24
Day 3 versus pre	16	− 1 (−9, 4)	0.17
Day 4 versus pre	12	− 11 (−16, −3)	0.02
Minimum heart rate (bpm)			
Day 1 versus pre	18	− 5 (−20, 3)	0.11
Day 2 versus pre	18	− 6 (−27, 0)	0.01
Day 3 versus pre	17	− 10 (−25, −5)	0.001
Day 4 versus pre	13	− 13 (−30, −5)	0.001
Maximum heart rate (bpm)			
Day 1 versus pre	18	− 4 (−16, 3)	0.62
Day 2 versus pre	18	− 14 (−27, 0)	0.004
Day 3 versus pre	17	− 8 (−35, −3)	0.01
Day 4 versus pre	13	− 26 (−45, 0)	0.02
Minimum central venous pressure (mmHg)			
Day 1 versus pre	9	− 1 (−2, 1)	0.32
Day 2 versus pre	9	− 2 (−3, 0)	0.06
Day 3 versus pre	7	− 2 (−3, −2)	0.04
Day 4 versus pre	5	0 (−4, 0)	0.41
Maximum central venous pressure (mmHg)			
Day 1 versus pre	9	− 1 (−1, 1)	0.33
Day 2 versus pre	9	− 1 (−3, 0)	0.62
Day 3 versus pre	7	− 2 (−3, −1)	0.06
Day 4 versus pre	5	− 4 (−4, −1)	0.10

bpm = beats per minute

Haemodynamic parameters (days 1–4 on nesiritide) compared with pre-baseline or baseline values. Bonferroni's correction for multiple comparisons lowered the required p-value to 0.013 to meet criteria for statistical significance

collected over a 3-year period were analysed, which consisted of a total of 18 separate infusions with each infusion occurring during separate hospitalisations. Of the 11 patients, two of them died. Among them, one patient presented on day of life 11 with hypoplastic left heart syndrome, cardiogenic shock, multiorgan system failure, and grade 3 intraventricular haemorrhage. The patient was medically managed and stabilised; however, the parents withdrew medical support 5 days after admission. The second patient presented at 5 months of age with severe re-coarctation and cardiogenic shock. Nesiritide was used following balloon dilation of the coarctation after which he underwent the Glenn procedure. The patient expired 4 months after the Glenn procedure from sepsis and multiorgan system failure.

Nesiritide dosing and inotropic support

The initial nesiritide dose was 0.01 μg/kg/minute; the median maximum dose was 0.02 μg/kg/minute (0.02, 0.03); and the median treatment duration was 111 hours (77, 204). There was no significant relationship between the maximum dose and the duration of nesiritide infusion as well as decrease in stage of acute kidney injury, which was last compared with baseline stage (p = NS). Similarly, there was no significant relationship between the vasoactive–inotropic score and the change in stage of acute kidney injury (p = NS). At no time point was the medication discontinued for hypotension.

Haemodynamics

The haemodynamic changes are listed in Table 3. There was a significant decrease in the minimum and maximum heart rate values and a trend towards a significant decrease in the maximum systolic blood pressure and minimum and maximum central venous pressures during the initial 4 days of therapy.

Urine output

There was a trend towards a significant increase in urine output throughout the course of therapy, however, it did not reach statistical significance

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Table 4. Changes in renal parameters during treatment.

Comparison	Pairs	Median (25th–75th %)	p-value
Urine output (ml/kg/hour)			
Day 1 versus pre	16	0.5 (−0.8, 3.6)	0.21
Day 2 versus pre	16	1.5 (0.6, 2.2)	0.03
Day 3 versus pre	15	1.4 (−0.3, 3.3)	0.13
Day 4 versus pre	11	1.6 (0.5, 2.3)	0.10
Creatinine (mg/dl)			
Day 1 versus pre	17	− 0.10 (−0.40, 0.10)	0.23
Day 2 versus pre	17	− 0.14 (−0.30, 0.0)	0.13
Day 3 versus pre	15	− 0.12 (−0.35, −0.10)	0.09
Day 4 versus pre	9	− 0.01 (−0.30, −0.10)	0.12
Day 5 versus pre	7	− 0.03 (−0.40, −0.15)	0.30
Last day versus pre	18	− 0.26 (−0.50, 0.0)	0.02
KDIGO stage			
Day 1 versus pre	17	− 1 (−1.0, 0.0)	0.08
Day 2 versus pre	17	− 1 (−1.0, 0.0)	0.15
Day 3 versus pre	15	− 1 (−1.0, 0.0)	0.12
Day 4 versus pre	9	− 1 (−2.0, 0.0)	0.11
Day 5 versus pre	7	− 2 (−2.0, 0.0)	0.17
Last day versus pre	18	− 1 (−2.0, 0.0)	0.03

KDIGO = Kidney Disease: Improving Global Outcomes stage of acute kidney injury
Renal parameters (days 1–5 and last day of therapy) compared with pre-baseline or baseline values. Bonferroni's correction for multiple comparisons lowered the required p-value to 0.013 for urine output and to 0.008 for creatinine and KDIGO stage in order to meet criteria for statistical significance

(when comparing day 4 to baseline: 1.6 ml/kg/hour [0.5, 2.3], p = 0.10, Table 4).

Serum creatinine and acute kidney injury staging

There was a significant decrease in serum creatinine (−0.26 mg/dl [−0.50, 0.0], p = 0.02) and a significant decrease in the stage of acute kidney injury (−1 [−2.0, 0.0], p = 0.03) when comparing the last day of therapy with baseline values (Table 4). The number of patients who experienced a decrease in the stage of acute kidney injury of 2 or more – where a change in the stage of acute kidney of 2 or more was possible, that is, baseline stage >1 – was significant (five of 12, 42%, p < 0.001) (Table 5 and Fig 1). Serum creatinine levels and stage of acute kidney injury before therapy and on the last day of therapy are listed for each patient in Table 6.

Hypoplastic left heart syndrome

Our findings in patients with hypoplastic left heart syndrome were similar to those of the entire cohort of patients with critical CHD despite the relatively smaller number of patients (n = 6) and infusions (n = 12). The number of patients who experienced a decrease in the stage of acute kidney injury of 2 or more – where a change in the stage of acute kidney disease of 2 or more was possible, that is, baseline stage >1 – was significant (five of seven, 71%, p < 0.001).

Table 5. Changes in Kidney Disease: Improving Global Outcomes (KDIGO) stage of acute kidney injury.

Subgroup	Change in stage	n (%)	p-value
All patients (n = 18)	Decreased ⩾2	5 (28)	<0.001
	Increased ⩾2	1 (6)	0.60
Baseline stage >1 (n = 12)	Decreased ⩾2	5 (42)	<0.001
Baseline stage <2 (n = 6)	Increased ⩾2	1 (17)	0.26

Significant improvements were noted in KDIGO stage in all patients, irrespective of baseline KDIGO stage. By analysing patients in whom a change in stage of acute kidney injury of ⩾2 was possible (i.e., baseline stage >1), almost half of the patients (42%) demonstrated improvement

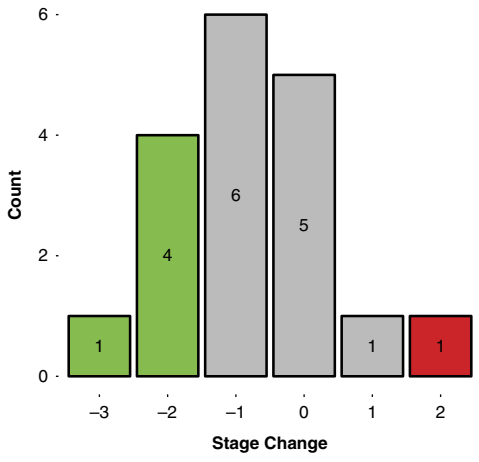

Figure 1.
Change in Kidney Disease: Improving Global Outcomes stage of acute kidney injury.

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Table 6. Creatinine and Kidney Disease: Improving Global Outcomes (KDIGO) values for each infusion.

Infusion run	Cr, baseline	Cr, end of therapy	KDIGO, baseline	KDIGO, end of therapy
1	0.6	0.5	1	0
2	0.5	0.4	1	0
3	1.0	0.3	3	0
4	1.0	0.5	3	2
5	0.3	0.3	0	0
6	0.5	0.6	2	2
7	1.1	0.3	2	0
8	0.4	0.3	1	0
9	1.3	1.3	3	3
10	1.0	0.3	2	0
11	1.4	1.1	3	3
12	1.4	0.9	3	2
13	1.7	0.6	3	1
14	0.3	0.5	0	2
15	0.6	0.9	1	2
16	0.7	0.4	3	1
17	0.9	1.0	2	2
18	0.5	0.4	2	1

Cr = creatinine (mg/dl)

Discussion

The use of nesiritide was not associated with worsening renal function in our cohort of patients with critical CHD throughout therapy. Previous studies in children have also demonstrated no worsening of renal function; however, these studies were limited by a short time period of observation (24–72 hours), much shorter compared with trials with meta-analyses in adults.[6–10] Previous studies have demonstrated that changes in serum creatinine lag behind changes in glomerular filtration rate by 48–72 hours,[14] and the delay may be even greater in patients with underlying renal dysfunction.[15]

We did find, however, that the stage of acute kidney injury improved significantly during nesiritide infusion. Jefferies et al[7] reported a significant decrease in serum creatinine by 72 hours (1.1–1.0 mg/dl) for the entire patient population. It is difficult to determine, however, the clinical significance of an absolute change in serum creatinine when considering the wide range of ages in the study and the fact that normal serum creatinine values change considerably over the first several months of life because of maturational changes in renal function.

A challenge in using acute kidney injury criteria, as pointed out in The Kidney Disease: Improving Global Outcomes clinical practice guidelines[11] and by other investigators,[16–20] is determining baseline – that is, before presentation/acute illness – kidney function. In our study, patients had severe CHD, and the vast majority of patients were less than several weeks of age. The challenges in determining baseline kidney function in this cohort of patients were compounded by the fact that normal serum creatinine values change considerably over the first several weeks to months of life because of maturational changes in renal function. We utilised normative values of serum creatinine indexed to narrow age intervals (weeks 1–4 and months 2–12)[13] to determine the baseline stage of acute kidney injury, and we used the *same approach* to determine the stage of acute kidney injury during nesiritide infusion.

It is unclear to what extent, if any, the decrease in stage of acute kidney injury can be attributed to the use of nesiritide. Nesiritide may favourably impact renal function by increasing renal perfusion as it improves stroke volume and cardiac output by reducing ventricular afterload. This may be of particular importance in patients with single-ventricle physiology, where the pulmonary and systemic circulations are in parallel rather than in series, and the relative resistance between the two circuits determines the distribution of cardiac output between pulmonary and systemic circulations.[21–23]

Heart failure induces neurohormonal activation, leading to vasoconstriction of renal afferent and efferent arterioles and a decrease in the glomerular filtration rate. Natriuretic peptides exert a systemic and regional (renal) sympathoinhibitory effect that leads to vasodilation of afferent arterioles and a significant increase in the glomerular filtration rate and filtration fraction.[24,25] Nesiritide is a viable alternative for increasing urine output in patients with diuretic resistance due to chronic exposure to loop and thiazide diuretics.[26] Following the Fontan procedure, neurohormonal pathways are stimulated, and many of these patients are diuretic resistant, both of which provide a theoretical indication for the use of nesiritide. Costello et al[27] conducted a randomised, double-blinded, placebo-controlled trial of nesiritide in children undergoing the Fontan procedure. There was no difference between groups in primary outcome measures such as days alive and out of the hospital within 30 days of surgery; however, patients receiving nesiritide had appreciably greater urine output, but the finding was not statistically significant. Another important consideration in the selection of vasoactive agents to treat patients with cardiac disease is their impact on heart rate. Afterload-reducing agents such as nitroglycerin and nitroprusside induce a compensatory increase in cardiac sympathetic activity due to baroreceptor unloading, leading to increased heart rate.[28] Not only is nesiritide not associated with a compensatory increase in sympathetic activity but it has also been shown to directly inhibit systemic and myocardial sympathetic activity.[29] We found a significant decrease in heart rate during nesiritide infusion.

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There are several limitations to this study. Even though there was a protocol for using nesiritide and monitoring renal function, this was a retrospective analysis. The patient population was heterogenous with a variety of anatomical substrates producing single-ventricle physiology. The number of patients studied was small, and despite this fact nesiritide had a significant beneficial impact on haemodynamic parameters and stage of acute kidney injury. As discussed above, our ability to determine the baseline stage of acute kidney injury was limited; however, we applied the same approach in determining the baseline stage of acute kidney injury and the stage of acute kidney injury while receiving nesiritide. Maternally derived creatinine may have been a confounding factor; however, nesiritide was not used in newborns less than 7 days of age – a time frame where maternally derived creatinine should be completely cleared. Finally, even though we did not determine fluid balance during the nesiritide infusion, urine output increased, and the central venous pressure decreased, making it unlikely that the progressive decline in serum creatinine levels was due to an increase in intravascular volume.

Conclusion

Nesiritide had a favourable impact on haemodynamics and urine output in children with critical CHD and pulmonary congestion, and there was no associated worsening of renal function.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committee of the Children's Hospital of Orange County.

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