Perioperative Effects and Safety of Nesiritide Following Cardiac Surgery in Children

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Nesiritide (Natrecor, Scios Inc), human B-type natriuretic peptide, has hemodynamic effects that may be beneficial in pediatric patients after cardiac surgery. Experience with nesiritide and pediatrics is limited. The purpose of this study was to evaluate perioperative effects and safety of nesiritide in pediatric cardiothoracic surgery. Seventeen patients with congenital heart disease undergoing cardiac surgery were given a loading dose (1 µg/kg) while on cardiopulmonary bypass (constant flow) followed by continuous infusion for 24 hours (0.01 µg/kg/min × 6 hours, then 0.02 µg/kg/min × 18 hours). A 7% decrease in mean blood pressure was seen following nesiritide loading dose on cardiopulmonary bypass. No patient required intervention for hypotension while receiving nesiritide load or infusion. Nesiritide load during surgery and continuous infusion after cardiac surgery in pediatric patients resulted in no significant hemodynamic compromise.

Key words: *B-type natriuretic peptide, cardiac surgery, congenital heart disease, pediatrics*

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Nesiritide (Natrecor, Scios Inc, San Francisco) is a human B-type natriuretic peptide (BNP) produced by recombinant DNA technology. Endogenous BNP is produced by the cardiac ventricles in response to pressure or volume overload. Recombinant BNP, nesiritide, is composed of the identical 32-amino acid sequence as endogenous BNP. The end-organ pharmacologic actions of BNP include hemodynamic, neurohormonal, and renal effects.

The hemodynamic effects result in the therapeutic benefits of venous, arterial, and coronary vasodilation including decreased preload and afterload, decreased pulmonary capillary wedge pressure, decreased central venous pressure, decreased pulmonary arterial pressure, and decreased systemic vascular resistance [1-4]. Neurohormonal effects favorably inhibit the renin-angiotensin-aldosterone system, leading to decreased plasma aldosterone and norepinephrine levels [1-4]. Renal effects include increased urine output and lower diuretic utilization as well as an indirect effect on natriuresis attributable to suppression of the antinatriuretic hormonal action of the renin-angiotensin-aldosterone system [1-4]. These pharmacological properties of BNP make it a potentially useful agent in the management of cardiac surgical pediatric patients with ventricular dysfunction and/or renal insufficiency.

To date there are limited data regarding the use and safety of nesiritide in pediatric patients undergoing surgery for congenital heart disease [5,6]. The purpose of this study was to evaluate the perioperative effects and safety of nesiritide in pediatric patients following cardiothoracic surgery and cardiopulmonary bypass.

Materials and Methods

Patients

The study was approved by the Ministry of Health, Santo Domingo, Dominican Republic, and Heart Care International. Patients with tetralogy of Fallot (TOF), ventricular septal defect (VSD), and congenital heart defects resulting in elevated intracardiac filling pressures who underwent cardiac surgery as part of Heart Care International in January and February 2004 were considered candidates for the study. These particular defects were chosen because the postoperative course may be complicated by diastolic dysfunction or low cardiac output. Hemodynamic variables were reviewed for the first 24 postoperative hours for the 20 patients who were included in the study. Three patients were excluded from further analysis secondary to postoperative junctional ectopic tachycardia (n = 1) and sepsis (n = 2). Hemodynamic data from the remaining 17 patients were evaluated.

The median age was 8 years (range 0.3-14 years), and median weight was 21 kg (range 4-55 kg). Surgical procedures included repair of TOF (n = 9), repair of VSD (n = 7), and mitral valve repair (n = 1). Six of the 9 patients who underwent repair of TOF had a transannular patch as part of the repair. The mean cardiopulmonary bypass time was 130 ± 56 minutes; mean cross-clamp time was 70 ± 48 minutes. Hospital survival for the study patients was 100%.

Study Protocol

Each patient was started on nesiritide in the operating room, after completion of the surgical repair and before weaning from cardiopulmonary bypass. A loading dose of 1 μg/kg was administered over 10 to 15 minutes while patients were on cardiopulmonary bypass, maintaining constant flow. The mean blood pressure was recorded before and after the loading dose in 14 of the 17 patients. A continuous infusion was maintained for 24 postoperative hours in all patients (0.01 μg/kg/min × 6 hours and then 0.02 μg/kg/min × 18 hours).

Arterial blood gases and arterial blood pressures were determined from radial or femoral arterial catheters. Systemic oxygen saturation was measured by extremity pulse oximetry. Central venous pressure was measured via central venous catheter placed in the internal jugular or femoral vein. All monitoring lines were placed in the operating room. All patients were on continuous electrocardiograph monitors. Hemodynamic data were recorded over the first 24 postoperative hours.

Statistics

Results are shown as mean ± standard deviation. Comparisons were made using a paired *t* test. Statistical significance was defined as $P < .05$.

Results

Nesiritide Loading Dose on Cardiopulmonary Bypass

The mean blood pressure on cardiopulmonary bypass prior to the nesiritide loading dose was 54 ± 12 mm Hg. The mean blood pressure on cardiopulmonary bypass (no change in flow) after the nesiritide loading dose was 50 ± 12 mm Hg. Mean blood pressure decreased by 7% ± 7% after the nesiritide loading dose ($P = .003$, 14 of 17 patients, Table 1).

Perioperative Course

In 15 of 17 patients, nesiritide was the only postoperative medication; 2 patients also received milrinone (Table 1). All patients received their cell saver blood during the first 4 postoperative hours. No patient required additional volume or inotropic support during the nesiritide loading dose or in the intensive care unit (ICU) during the continuous infusion. Furosemide (1 mg/kg/dose every 6-12 hours) was started on postoperative day 1 in all patients. One patient had surgical heart block requiring dual-chamber pacemaker pacing via temporary pacing wires. This patient had return of sinus rhythm before hospital discharge. None of the other patients had arrhythmias that required intervention. Isolated premature atrial or ventricular beats were not considered arrhythmias. The mean total input, over the first 24 postoperative hours, was 82 ± 41 cc/kg/d; mean urine output was 4 ± 2 cc/kg/h (Table 1).

Two of the 17 patients continued nesiritide infusion past the 24-hour study period. The first patient

Table 1. Results Summary

Patient	Age (y)	Defect	Bypass Time (min)	Cross-Clamp Time (min)	mBP Before Nesiritide Load (mm Hg)	mBP After Nesiritide Load (mm Hg)	Maximum Inotropic Score	Mean 24-h Output (cc/kg/h)
1	2	TOF	107	67	36	36	0	4.7
2	3	TOF	84	61	46	42	0	6.0
3	1	VSD	95	58	44	40	0	4.1
4	10	MR	59	34	NA	NA	0	0.0
5	6	VSD	188	0	56	57	0	3.3
6	14	TOF	106	67	68	70	0	2.9
7	0.5	VSD	187	40	44	40	5	5.1
8	2	VSD	85	39	48	44	0	3.1
9	9	VSD	120	81	56	52	0	2.7
10	11	TOF	120	53	48	48	0	5.4
11	11	TOF	183	129	85	75	0	0.9
12	6	TOF	175	108	52	48	0	2.5
13	12	VSD	135	83	NA	NA	0	3.7
14	11	TOF	102	78	61	61	0	0.7
15	0.3	VSD	89	47	60	54	0	7.4
16	10	TOF	283	217	50	38	7	3.1
17	8	TOF	92	35	NA	NA	0	5.9

mBP – mean blood pressure; TOF – tetralogy of Fallot; VSD – ventricular septal defect; MR – mitral valve regurgitation; NA, not applicable.

underwent repair of TOF with transannular patch and had signs of diastolic dysfunction, elevated central venous filling pressures, pleural effusion, and peripheral edema on postoperative day 1. The second patient underwent repair of VSD and had volume overload that was treated with an additional day of nesiritide plus diuretics.

Patients With TOF

Secondary to the significant number and age profile of our patients with TOF, they were compared with those patients with other defects (VSD, MR; Table 2). Preoperative oxygen saturation (TOF 84% ± 9% vs other 97% ± 6%; $P = .003$) and cross-clamp time (TOF 91 ± 55 minutes vs other 48 ± 27 minutes; $P = .03$) were the only variables that were significantly different between the 2 groups. The other variables did not reach statistical significance.

Discussion

Following cardiopulmonary bypass, catecholamines, endothelin, renin-angiotensin-aldosterone, and other neurohormonal systems are up-regulated [7] similar to the up-regulation of the neurohormonal system seen in patients with congestive heart failure [8]. The up-regulation of these neurohormones results in fluid retention and elevation of both systemic and pulmonary vascular resistance [9,10]. The body compensates for these neurohormonal changes by activating the natriuretic hormonal system [11]. The natriuretic hormones, BNP and others, bind to natriuretic peptide receptors resulting in the production of intracellular cyclic guanosine monophosphate (cGMP), which promotes vasodilation and natriuresis [11].

Several studies have examined the natriuretic hormonal system's response to cardiopulmonary bypass in children. Yoshimura et al [12] documented an increase in BNP in children following repair of tetralogy of Fallot and Fontan operation. Costello et al [13] examined changes in the natriuretic hormone system in 5 infants with congenital heart disease characterized by left-to-right intracardiac shunt during and after cardiopulmonary bypass. Costello's study demonstrated an increase in BNP following cardiopulmonary bypass compared with baseline [13]. This elevation was attributed to transient myocardial dysfunction related to cardiopulmonary bypass. Interestingly, despite the increase in the natriuretic peptides after cardiopulmonary bypass, this study showed a decrease in the calculated biological activity of the natriuretic hormone system [13]. The molar ratio of cGMP/BNP and cGMP/(atrial natiuretic peptide + BNP + dendroaspis natriuretic peptide) was used to assess the biological activity of the natriuretic hormone system [13]. The mechanisms responsible for the impairment of the natriuretic hormonal system following cardiopulmonary bypass are unknown. Potential etiologies include hypothermia, exclusion of the heart from circulation during cardiopulmonary

Table 2. Comparison of Patients With TOF to the Other Patients in the Study (VSD, MR)

	TOF	Other	*P* Value
N	9	8	
Age (y)	8.5 ± 4	5 ± 4.6	.07
Preoperative oxygen saturation (%)	84 ± 9	97 ± 6	.003
Cardiopulmonary bypass time (min)	139 ± 64	120 ± 48	.2
Cross clamp time (min)	91 ± 55	48 ± 27	.03
mBP before nesiritide load (mm Hg)	56 ± 15	51 ± 7	.2
mBP after nesiritide load (mm Hg)	52 ± 15	48 ± 7	.2
Maximum inotropic score	0.8 ± 2	0.6 ± 2	.4
Mean 24-h urine output (cc/kg/h)	3.6 ± 2	3.7 ± 2	.5

TOF – tetralogy of Fallot; VSD – ventricular septal defect; MR – mitral valve regurgitation; mBP – mean blood pressure.

bypass, or the underlying cardiac abnormality. The clinical significance of postoperative impairment of the natriuretic hormonal system may be significant because cardiopulmonary bypass is associated with fluid retention and increased systemic and vascular resistance [9,10]. These perioperative disturbances in the natriuretic hormonal system lead us to speculate that this patient population may benefit from pharmacologic intervention with exogenous BNP, nesiritide.

The hemodynamic effects of nesiritide are characterized by balanced venous and arterial dilation as well as natriuresis and diuresis [1-4]. Clinical studies in the adult heart failure population have demonstrated a reduction of preload and afterload as evidenced by a reduction of pulmonary capillary wedge pressure, right atrial pressure, pulmonary arterial pressure, and systemic vascular resistance [1-4]. Cardiac index increased secondary to afterload reduction in a dose-dependent manner, because nesiritide exerts no direct positive inotropic actions [1-4].

Nesiritide also decreases sympathetic stimulation; inhibits the renin-angiotensin-aldosterone system, leading to decreased plasma aldosterone and norepinephrine levels; and decreases cardiac preload without resultant reflex tachycardia [1-4]. In the renal vasculature, nesiritide vasodilates the renal afferent and efferent arteries and increases glomerular filtration, diuresis, and natriuresis [1-4]. Renal effects include increased urine output and lower diuretic utilization.

All of the above hemodynamic and neurohormonal effects of nesiritide are desirable in patients with fluid retention and increased systemic and vascular resistance following cardiopulmonary bypass. Nesiritide delivers central hemodynamic benefits without inflicting the risk of renal damage, arrhythmia, or tachycardia. Nesiritide may offer therapeutic advantages when compared with commonly used inotropic agents. Unlike inotropic agents, nesiritide lacks proarrhythmic and chronotropic properties, and it does not increase myocardial oxygen demand [14]. It is also less likely to decrease blood flow to the peripheral organs (ie, lower risk of postoperative renal compromise).

In our study population, after the loading dose on cardiopulmonary bypass maintaining constant flow, the mean blood pressure decreased by 7% ± 7% compared with baseline. This initial decrease in mean blood pressure following the loading dose was believed to provide beneficial afterload reduction without hypotension. No hypotension requiring clinical intervention was noted during the postoperative nesiritide infusion in the ICU. None of our patients required additional volume or inotropic support during or after the loading dose of nesiritide. However, all of our patients received their cell saver blood during the first 4 postoperative hours in the ICU.

The diuretic effect of nesiritide was believed to be clinically important. Urine output was 4 ± 2 cc/kg/h over the first 24 postoperative hours. Unfortunately, and a limitation of the study, there was no control group for comparison. All of our patients were all started on furosemide (1 mg/kg/dose every 6-12 hours) on postoperative day 1. Therefore, we cannot comment on decreased diuretic utilization as is noted in the adult population with chronic heart failure treated with nesiritide [14].

Our study had a significant number of patients with TOF. These patients were older than the usual patient with TOF who presents for repair secondary to the limitations of cardiac surgery for children in the Dominican Republic. There was no difference in effect and safety profile of nesiritide in these patients compared with the rest of our patient population.

The pharmacologic profile of nesiritide is attractive in the postoperative setting. The drug has a rapid onset of action and a relatively short half-life of 18 minutes. In adults, cardiovascular effects dissipate within 2 to 4 hours after discontinuation of the drug. Nesiritide is cleared by receptors on cell sur-

faces with endocytosis and lysosomal degradation, as well as proteolysis by circulating neural endopeptidases [15,16]. The drug is not primarily cleared by the kidneys or the liver; therefore, dose adjustment in patients with renal or hepatic insufficiency is not necessary. Concomitant use of oral or intravenous cardiac medications does not alter the pharmacokinetics of nesiritide in adults. The drug may be administered via a peripheral intravenous line.

Along with the previously mentioned limitations, this study was limited by the small sample size and age of sample, because it is unusual to perform TOF repair in children with the mean age of 8 years. Also, we were unable to compare changes in central venous pressure and pulmonary arterial pressure secondary to nesiritide, because the drug was started while the patient was still on cardiopulmonary bypass. Central venous pressure monitoring lines were removed in all patients before discontinuation of nesiritide. BNP levels were not obtained in the current study because the laboratory test is not available in the Dominican Republic.

Conclusion

A 7% decrease in mean blood pressure was seen following nesiritide loading dose on cardiopulmonary bypass resulting in beneficial afterload reduction. Furthermore, the nesiritide loading dose during cardiac surgery and the continuous infusion after surgery in pediatric patients resulted in no significant hemodynamic compromise. The perioperative disturbances in the natriuretic hormonal system lead us to speculate that this patient population may benefit from pharmacologic intervention with exogenous BNP, nesiritide. Given its lack of adverse hemodynamic effects, prospective comparisons with other agents in this population appear warranted.

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