Title: Nicardipine for Hypertension following Aortic Coarctectomy and Superior

Cavopulmonary Anastomosis

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Abstract

Background: Literature on the use of nicardipine, a dihydropyridine calcium channel antagonist, in children recovering from cardiac surgery is sparse and, to our knowledge, non-existent in children with single ventricle anatomy. We aimed to report our experience with nicardipine in these patient populations.

Methods: We performed a retrospective review of children recovering from aortic coarctectomy and superior cavopulmonary anastomoses who received nicardipine for hypertension at our institution between 2007-2013. Hemodynamic variables prior to and after nicardipine initiation were compared using paired t-tests.

Results: Seven children recovering from aortic coarctectomy (median age 8.6 months, range: 1.5 months - 7.9 years) and four children recovering from superior cavopulmonary anastomosis (median age 7 months, range: 5 - 9 months) were reviewed. For all patients, at 6 hours after initiation of nicardipine, mean systolic blood pressure was significantly decreased, 123 ± 19 mmHg versus 103 ± 14 mmHg (P=0.001), as were diastolic blood pressure, 68 ± 20 mmHg versus 53.5 ± 10 mmHg (P=0.041), and sodium nitroprusside dose, 4.3 ± 2.9 mcg/kg/min versus 1.3 ± 1.7 mcg/kg/min (P=0.002).   Further, within 24 hours, serum lactate decreased from 1.45 ± 0.82 mg/dL to 0.81 ± 0.29 mg/dL (P=0.016). Heart rate, blood urea nitrogen and serum creatinine measurements were statistically unchanged.

Conclusions: Nicardipine effectively decreased blood pressure without apparent adverse events in a small cohort of children with postoperative hypertension while recovering from aortic coarctectomy and superior cavopulmonary anastomosis. Further

research comparing nicardipine to more conventional titratable anti-hypertensive agents in these patient populations is warranted.

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Introduction

Hypertension is a relatively common complication following surgery for congenital heart disease, especially in the immediate postoperative period, for patients recovering from aortic coarctectomy (1-2) and superior cavopulmonary anastomoses (3-4). For these children, titratable intravenous anti-hypertensive medications are the mainstays of therapy. Sodium nitroprusside and esmolol are most commonly implemented and most extensively studied (5-6). Both of these agents however have potential undesirable side effects. Sodium nitroprusside is a nitric oxide donor that is quickly metabolized *in vivo* to cyanide and thiocyanate, both of which have been shown to accumulate with standard dose infusions (7-8). Additionally, sodium nitroprusside is a potent venodilator that often requires volume loading to maintain adequate cardiac preload. Esmolol, a beta-adrenergic antagonist, could cause acute myocardial depression or exacerbate underlying reactive airway disease. Perhaps most importantly, in some cases, hypertension will persist despite implementation of one or both of these agents. For these reasons, alternative titratable agents should be explored.

We aimed to report our experience using nicardipine, a dihydropyridine calcium channel antagonist, for hypertension in infants and children recovering from aortic coarctectomy and superior cavopulmonary anastomoses. We hypothesized that a review of our experience would demonstrate nicardipine to be an effective agent in these patient populations without apparent unwanted clinical effects.

Patients and Methods

This retrospective study was approved by the Institutional Review Boards at Wayne State University and the Detroit Medical Center. Due to the retrospective nature of the study, the need for informed consent was waived. All children who received nicardipine for hypertension following aortic coarctectomy and superior cavopulmonary anastomosis at our institution from 2007-2013 were reviewed. Patient characteristics such as age at surgery, underlying cardiac diagnosis, and durations of cardiopulmonary bypass and aortic cross-clamping were recorded. Hemodynamic parameters (e.g. systolic and diastolic pressure, heart rate), dose of sodium nitroprusside infusion, and dose of esmolol immediately prior to nicardipine initiation and six hours after initiation of the infusion were recorded. Arterial lactate, blood urea nitrogen (BUN), and creatinine measurements prior to and during the 24 hours subsequent to nicardipine initiation were also recorded.

Data are provided as mean with standard deviation for normally-distributed continuous variables and median with range for skewed continuous variables. Data before and after initiation of nicardipine infusion were compared using paired student t-tests

Results

Eleven patients who received nicardipine for hypertension following pediatric cardiac surgery were identified and reviewed. Four of the patients were infants with single ventricle anatomy recovering from their superior cavopulmonary anastomoses and seven patients were children with coarctation of the aorta who had undergone aortic

coarctectomy. These patients are summarized in Table 1. Median ages of children undergoing superior cavopulmonary anastomoses and coarctectomy were 7 months (range: 5 months - 9 months) 8.6 months (range: 1.5 months - 7.9 years), respectively. Transesophageal echocardiograms performed intraoperatively following cardiopulmonary bypass were available for the four study patients who underwent superior cavopulmonary anastomoses and reported normal single ventricle function.

All patients were receiving sodium nitroprusside, esmolol, or both for postoperative hypertension at the time of nicardipine initiation. Median timing of nicardipine initiation for all patients was postoperative day 1 (range: 0 - 6). Initial nicardipine dose was 0.5 mcg/kg/min in all patients, and the median maximum nicardipine dose used was 2.75 mcg/kg/min (range: 1 - 5 mcg/kg/min). Median duration of nicardipine infusion was 33 hours (range: 12 - 96 hours). Mean systolic and diastolic blood pressure, heart rate, nitroprusside and esmolol dose, arterial lactate, BUN and creatinine before initiation of nicardipine infusion and after nicardipine infusion are provided in Table 2. Mean systolic and diastolic blood pressure, and sodium nitroprusside dose were significantly decreased within 6 hours of nicardipine infusion while mean heart rate was relatively unchanged. Within 24 hours, arterial lactate was significantly decreased, and mean BUN and creatinine values were statistically unchanged from pre-infusion measurements. Changes in systolic blood pressure immediately before and six hours after initiation of nicardipine infusion for individual patients are illustrated in Figure 1.

Discussion

Hypertension following aortic coarctectomy has been well-described (1-2). The pathophysiology of this hypertension is multi-factorial though has been primarily ascribed to alterations in baroreceptor stimulation leading to excessive sympathetic nervous system activity (2). In our patients, nicardipine not only effectively reduced systolic and diastolic blood pressure but also permitted, in many cases, weaning of sodium nitroprusside and esmolol infusions. Use of an arteriolar vasodilator such as nicardipine should be physiologically appropriate for these patients, considering excessive sympathetic nervous system activity predominantly leads to release of the potent vasoconstrictor norepinephrine and stimulation of the renin-angiotensin-aldosterone axis. In addition to our experience, use of nicardipine after aortic coarctectomy has been reported in three other small case series. In 1993, Treluyer et al provided the first report of nicardipine hypertension in pediatric patients, a case series of 14 children, 5 of which were cardiac patients recovering from aortic coarctectomy (9). In 2001, Tobias published the first report of nicardipine use exclusive to children recovering from cardiac surgery. This series contained 9 patients, all with two ventricle anatomy, and 3 of which had underwent aortic coarctectomy (10). In 2004, Nakagawa and colleagues published the first, and to our knowledge, only study devoted exclusively to the use of nicardipine in patients recovering from aortic coarctectomy, N=10 (11). In all of these reports, nicardipine was effective at lowering blood pressure without any detectable clinical side effects. Yet despite a sound physiologic rationale for its use and encouraging early observational experiences, no further research focused on nicardipine use in this patient population, to our knowledge, has been published.

Hypertension while recovering from superior cavopulmonary anastomoses has also been previously reported (3-4). The pathophysiology of hypertension in these patients has been postulated to primarily be a compensatory response to increased cerebral systemic venous pressures. Sodium nitroprusside has most commonly been reported as a first line agent in these patients. In an elegant study by Simsic et al, they demonstrated that reduction of arterial blood pressure using sodium nitroprusside did not alter cerebral autoregulation and thus did not adversely affect cerebral blood flow. On the other hand, adequate systemic venous pressure is required to maintain passive pulmonary blood flow in these patients, which could theoretically be adversely affected by a potent venodilator such as sodium nitroprusside. Nicardipine, which has little effect on systemic venous resistance (12), could offer a theoretical advantage to these patients. To our knowledge, this report is the first description of the use of nicardipine in infants with single ventricle anatomy.

Use of calcium-channel antagonists in infants and young children, especially those with cardiac disease, has historically been discouraged, in large part because of differences between the immature and adult myocardium. The neonatal myocardium has been shown to have a lower density of calcium channels (13) and reduced intracellular stores of calcium secondary to an underdeveloped T-tubule network (14). Consequently, the neonatal myocardium depends more so on extracellular calcium and is more sensitive to calcium channel blockade. For example, verapamil, a non-dihydropyridine calcium-channel antagonist, has been associated with cardiovascular collapse in neonates and

infants, even at therapeutic doses, and thus relatively contraindicated in this age group (15), though this notion has recently been questioned (16). Nicardipine, in contrast to verapamil and other non-dihydropyridine calcium channel antagonists, has greater selectivity for L-type calcium channels in vascular smooth muscle than in cardiac myocytes (12). This selectivity is related to the voltage-dependence of L-type calcium channels, such that the resting membrane potential of vascular smooth muscle cells is less negative than that of cardiac myocytes. As a result, nicardipine should have minimal effect on myocardial function. In fact, studies of nicardipine use in adults with myocardial dysfunction have demonstrated increased in cardiac index, decreased pulmonary capillary wedge pressure, and improved coronary blood flow (12). In our series, none of the patients, which includes 6 patients who were also receiving esmolol infusions at the time of nicardipine initiation, experienced hypotension, bradycardia, or signs of hypoperfusion while receiving nicardipine infusions. These data should encourage further investigation into the use of nicardipine in these children.

This study represents retrospective pilot data from a small single center case series. Nicardipine use in infants and children after cardiac surgery must be further studied before more widespread use can be recommended. Pharmacokinetic data are needed in this patient population in order to optimize dosing regimens. Moreover, studies comparing the efficacy and safety of nicardipine to sodium nitroprusside or esmolol following aortic coarctectomy or superior cavopulmonary anastomoses should be pursued. A multi-centered study randomizing infants with postoperative hypertension while recovering from these cardiac surgeries to one of these three agents would be

particularly helpful to the pediatric cardiac critical care community. With additional research, nicardipine could become an important part of the limited armamentarium of vasoactive medications available to cardiac intensive care providers.

Conclusions

In a small cohort of patients with biventricular and univentricular anatomy, nicardipine effectively reduced blood pressure without apparent adverse events in patients with hypertension after pediatric cardiac surgery.

Conflicts of Interest

None Declared

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None

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Table 1. Hemodynamic measurements and vasoactive medication doses before nicardipine infusion

Cardiac Lesion	Age (months)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	Nitroprusside (mcg/kg/min)	Esmolol (mcg/kg/min)
PA/IVS	8	133	81	132	4	0
HLHS	5	126	62	131	2	0
HLHS	6	98	40	100	7	0
HLHS	9	134	86	156	5	0
CoA	1	116	72	138	6	250
CoA	2	116	52	118	0	350
CoA	2	108	65	137	6	300
CoA	8	108	64	130	4	400
CoA	50	168	110	113	10	0
CoA	52	131	74	107	1	250
CoA	94	118	42	135	2	50

[a] PA/IVS: pulmonary atresia with intact ventricular septum; HLHS: hypoplastic left heart syndrome; CoA: coarctation of the aorta; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate

Table 2. Mean changes in hemodynamic variables before and after nicardipine initiation

Variable[a]	Pre-nicardipine	Post-nicardipine	P-value
Systolic BP (mmHg)	120 ± 5.8	101 ± 4.5	0.014
Diastolic BP (mmHg)	66 ± 5.8	53 ± 2.9	0.049
Heart Rate (bpm)	129.5 ± 5	125.5 ± 4.6	0.57
Nitroprusside (mcg/kg/min)	3.9 ± 0.9	1.2 ± 0.5	0.012
Esmolol (mcg/kg/min)[b]	225 ± 195	221 ± 149	0.89
Arterial lactate (mg/dL)	1.52 ± 0.25	0.87 ± 0.11	0.034
BUN (mg/dL)	13.9 ± 5.5	13 ± 6.3	0.72
Creatinine (mg/dL)	0.45 ± 0.15	0.43 ± 0.2	0.81

[a] Hemodynamic parameters and vasoactive medication doses represent values immediately prior to and six hours post-initiation of the infusion. Arterial lactate, blood urea nitrogen (BUN), and creatinine represent measurements prior to and during the 24 hours subsequent to initiation of the infusion.

[b] Contains measurements from only patients recovering from aortic coartectomy (n=7); no patients recovering from superior cavopulmonary anastomoses received esmolol.

Figure Legends

Figure 1. Changes in systolic blood pressure (BP) in patients recovering from aortic coarctectomy (black lines) and superior cavopulmonary anastomoses (gray lines) six hours after initiation of nicardipine infusion. Systolic BP was decreased in all but one post-coartectomy patient, in whom esmolol was aggressively weaned from 350 to 100 mcg/kg/min during this time period. Mean change in systolic BP was $-15.5 \pm 9.9\%$.