Use of Nicardipine After Cardiac Operations Is Safe in Children Regardless of Age

Matthew L. Stone, MD, PhD, John Kelly, MD, Maanasi Mistry, MD, Marcia Buck, PharmD, James Gangemi, MD, and Jeffrey Vergales, MD, MS

Divisions of Thoracic and Cardiovascular Surgery and Pediatric Cardiology, and Department of Pharmacology, The University of Virginia Health System, Charlottesville, Virginia

Background. **Control of postoperative hypertension is central to the care of infants and children after cardiac operations. Continuous pharmacologic delivery affords the advantage of rapid onset and ease of titration. Although well established in older children and adults, calcium channel blockers are routinely avoided in children aged younger than 1 year secondary to concerns of safety and efficacy in the setting of sarcoplasmic reticulum development. Thus, the purpose of this study was to review a single-institution experience with nicardipine, a selective calcium channel blocker, in pediatric patients after cardiac operations.**

Methods. **Children undergoing cardiac operations at the University of Virginia from 2010 to 2015 were retrospectively reviewed after selection based on receipt of nicardipine for blood pressure management in the postoperative period. Demographic, operative, laboratory, and postoperative data were collected for adverse effect analysis and outcomes comparisons between infants aged younger than 6 months (group 1) and older than 6 months (group 2).**

Results. **During the study period, 68 children (group 1: n = 33 [48%]; group 2: n = 35 [52%]) received nicardipine after cardiac operations (0.5 to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Nicardipine was initiated at a mean of 6.6 ± 13.1 hours postoperatively in group 1 and 5.4 ± 7.8 hours in group 2. Nine patients (13%) demonstrated clinically significant hypotension necessitating dosing titration with no statistically significant differences between groups. No major adverse events occurred following nicardipine administration.**

Conclusions. **Nicardipine is well tolerated after cardiac operations in children irrespective of age or underlying pathology. Thus, nicardipine should be considered as safe and effective in children of all ages for control of hypertension after cardiac operations.**

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Treatment of postoperative hypertension is fundamental to the care of infants and children after a cardiac operation. Paradoxical hypertension is estimated to occur in as many as 70% of children undergoing aortic coarctectomy, and 30% of children have persistent hypertension after the repair [1–3]. A persistence of autonomic dysregulation has been proposed as the predominate mechanism for the high incidences of postoperative hypertension, introducing the need for further standardization of treatment strategies in children to achieve postoperative normotension while avoiding the inherent risks of varied pharmacologic therapies [1].

To this aim, pharmacologic agents that are administered continuously support rapid onset of treatment and afford ease of titration in the postoperative period. Current treatment paradigms commonly adopt nitrodilators and β-blockers as the primary agents of choice for postoperative hypertension treatment, yet these agents carry a significant risk of cyanide toxicity, bronchospasm, and negative inotropic effects [4]. Thus, the purpose of this study was to evaluate the use of the selective calcium channel blocker nicardipine in the treatment of postoperative hypertension. Specific attention was paid to children aged younger than 6 months because calcium channel blockers have been traditionally avoided in this age group secondary to concerns for immature sarcoplasmic reticulum development.

Nicardipine was adopted for this study and the treatment of infants and children at our institution because it offers a selective vascular smooth muscle effect profile with minimal inotropic, chronotropic, and dromotropic effects on the myocardium compared with other agents, such as verapamil, which have more defined yet debated risk profiles for use in infants aged younger than 6 months. In addition, prior investigation has suggested that nicardipine use results in effective reduction in the mean arterial pressure while having no significant effect on the mean heart rate [5]. The present study extended application of nicardipine to all children at our institution undergoing congenital heart operations, because postoperative hypertension has been associated with an increased risk of stroke and adverse outcomes among diverse congenital heart disease pathologies [6].

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Address correspondence to Dr Stone, Division of Cardiothoracic Surgery, Department of Surgery, University of Virginia Health System, 1215 Lee St, PO Box 800679, Charlottesville, VA 22908; email: mstone@virginia.edu.

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Patients and Methods

Institutional IRB approval was obtained for the study, UVA IRB-HSR no. 17774.

A retrospective review was performed for children aged younger than 18 years undergoing cardiac operations at the University of Virginia from 2010 to 2015, with selection based on the receipt of nicardipine for the management of postoperative hypertension. A starting dose of 0.5 to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was used in accordance with previously published indicators, with titration as indicated by clinical response to treatment [7]. In addition, patients administered nicardipine received no concomitant antihypertensive agent apart from postoperative inotropic support with milrinone. The analysis excluded patients who received nicardipine while on extracorporeal membrane oxygenation (ECMO) support.

Demographic, operative, laboratory, and postoperative data were collected retrospectively to determine the prevalence of adverse events related to nicardipine use, and comparisons were performed between infants aged younger than 6 months (group 1) and older than 6 months (group 2). Postoperative hemodynamic variables were reviewed to include clinically relevant hypotensive episodes, defined as a temporary cessation or downward titration of nicardipine treatment. Titration of the nicardipine dose was at the clinical discretion of the provider and not based on a standard protocol.

Major adverse events, including stroke, dysrhythmia, cardiogenic shock, or death, were considered as failure of therapy. Comparisons were made between infants with and without adverse effects of nicardipine use to determine demographic, operative, and postoperative factors that may have contributed to disparate outcomes. Appropriate parametric, paired and nonpaired, descriptive statistical testing was performed for all continuous variables. Categoric variables were analyzed by χ^2 analysis and the Fisher's exact test, where appropriate.

Results

During the study period, 68 children, 33 in group 1 (48%) and 22 in group 2 (52%), received nicardipine after their cardiac operation. Children were more commonly boys (74%) with a median age of 0.7 years (interquartile range, 0.17 to 6.6 years; Table 1). Eight children (12%) were receiving antihypertensive agents preoperatively, and 27 (40%) required outpatient antihypertensive management at discharge. Postoperative nicardipine use most commonly followed aortic coarctation repair yet encompassed the treatment of a diverse range of congenital surgical pathologies (Table 2). Infants aged younger than 6 months were more commonly on preoperative antihypertensive management (Table 3). In addition, infants younger than 6 months had a longer postoperative ventilator requirement and postoperative total length of stay.

Change in systolic and diastolic blood pressure variables were similar when infants aged younger and older than 6 months were compared (Table 3). Nicardipine was initiated postoperatively at a mean timepoint of 6.6 ± 13.1 hours in group 1 and 5.4 ± 7.8 hours in group 2 respectively, with 22 children (33%) requiring initiation of therapy in the operating room. Clinically significant hypotension necessitating dose titration occurred in 13% of patients after nicardipine administration, with no significant difference between groups (group 1: n = 6 [17%], group 2: n = 3 [9%]; $p = 0.47$).

No significant major adverse events, including stroke, dysrhythmia, cardiogenic shock, or death were noted in either group. In addition, no patients receiving nicardipine required cessation of therapy, an additional antihypertensive agent, or transition to an alterative

Table 1. Baseline Demographics of the Study Population

Patient Characteristics[a]	Measure (N = 68)
Male	50 (74)
Race	
White	42 (62)
Black	17 (25)
Hispanic	7 (10)
Other	2 (3)
Age at operation, y	0.7 (0.17–6.6)
Weight at operation, kg	8.3 (4.4–22.8)
Antihypertensive medication	
Preoperatively	8 (12)
At discharge	27 (40)

[a] Categoric data are presented as number (%) and continuous data as median (interquartile range).

Table 2. Type of Cardiac Operation in Patients Receiving Nicardipine Postoperatively Stratified by Age

Operation	Group 1 <6 months (n = 33) No. (%)	Group 2 >6 months (n = 35) No. (%)
Coarctation repair	22 (66.7)	9 (25.7)
Subaortic AS resection		6 (17.1)
Heart transplant	4 (12.1)	1 (2.9)
Bidirectional Glenn	3 (11.0)	1 (2.9)
Aortic root replacement		4 (11.4)
Vascular ring repair	1 (3.0)	2 (5.7)
AVR/PVR		2 (5.7)
Supravalvular AS and arch augmentation		2 (5.7)
Aortic valve replacement		2 (5.7)
Anomalous coronary artery		1 (2.9)
Atrial septal defect repair		1 (2.9)
Fenestrated Fontan		1 (2.9)
Blalock-Taussig shunt	1 (3.0)	
Truncus arteriosus repair	1 (3.0)	
AVR/mitral commissurotomy		1 (2.9)
Aortic aneurysm repair		1 (2.9)
VSD/arch reconstruction	1 (3.0)	
Aortic arch reconstruction		1 (2.9)

AS = aortic stenosis; AVR = aortic valve replacement; PVR = pulmonary valve replacement; VSD = ventricular septal defect.