

CLINICAL INVESTIGATION

Clevidipine for Perioperative Blood Pressure Control in Infants and Children Undergoing Cardiac Surgery for Congenital Heart Disease

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OBJECTIVE To determine the efficacy and adverse effect profile of clevidipine when used for perioperative blood pressure (BP) control during surgery for congenital heart disease (CHD).

METHODS We retrospectively reviewed our experience with the perioperative use of clevidipine in pediatric-aged patients undergoing surgery for CHD.

RESULTS The study cohort included 14 patients ranging from 11 months to 15 years (7.4 ± 4.6 years) and weighing from 5 to 41 kg (21.8 ± 11.1 kg). Clevidipine was administered as a continuous infusion for control of either postoperative BP or intraoperative mean arterial pressure (MAP) during cooling and cardiopulmonary bypass (CPB). It was administered as a bolus for BP control during emergence from anesthesia following cardiac surgery. The continuous infusion was started at 1 mcg/kg/min and increased in increments of 0.5 to 1 mcg/kg/min as needed. For postoperative BP control, dosing requirements varied from 1 to 7 mcg/kg/min (mean = 2.0 ± 1.2 mcg/kg/min). The target BP was achieved within 5 minutes in all patients. Two patients were treated with intravenous or oral propranolol for an increase in heart rate (HR) while receiving clevidipine. Despite doses up to 10 mcg/kg/min, effective control of MAP could not be achieved during CPB and cooling (core body temperature 28°C to 32°C). Bolus doses of clevidipine (10 to 15 mcg/kg) controlled BP during emergence from anesthesia with a decrease of the MAP from 97 ± 6 mm Hg to 71 ± 5 mm Hg ($p < 0.01$).

CONCLUSIONS Clevidipine is effective for perioperative BP control in infants and children with CHD; however, it does not appear effective in controlling MAP during cooling and CPB.

Index Terms cardiothoracic surgery, clevidipine, congenital heart disease, pediatric, perioperative hypertension

Abbreviations BP, blood pressure; CPB, cardiopulmonary bypass; CHD, congenital heart disease; HR, heart rate; MAP, mean arterial pressure

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INTRODUCTION

Various factors may result in perioperative hypertension in the pediatric-aged patient including renal failure or insufficiency, volume overload,

or activation of the sympathetic nervous system from pain and agitation.^{1–3} Perioperative blood pressure (BP) control may be even more problematic and of greater consequence following surgery for congenital heart disease (CHD) where hypertension may result in excessive bleeding or disruption of suture lines. Once treatable causes of hypertension such as pain, hypercarbia, and hypoxemia are excluded, pharmacologic control of BP in adults may be indicated.

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During the perioperative period, there are several options for rapid BP control including the intravenous administration of sodium nitropruside, labetalol, nicardipine, and hydralazine.³⁻⁵ Clevidipine (Cleviprex, The Medicines Company, Parsippany, NJ) is a short-acting, intravenous calcium channel antagonist of the dihydropyridine class. It undergoes rapid metabolism by nonspecific blood and tissue esterases and has a half-life of 1 to 3 minutes. It is currently approved by the Food and Drug Administration for the reduction of BP when oral therapy is not feasible or desirable. To date, there are no published reports of its use in the perioperative care of pediatric-aged patients with CHD and only 1 report regarding its use in infants and children.⁶ We present our preliminary experience with the use of clevidipine for BP control in pediatric patients with CHD.

METHODS

This retrospective review was approved by the institutional review board of the University of Missouri. The patients described in this retrospective review were cared for during a trip of Heart Care International (Greenwich, Connecticut) to San Salvador, El Salvador. The use of clevidipine was formally approved by the Ministry of Health of El Salvador and by Heart Care International. As part of ongoing perioperative quality assurance measures, data were collected prospectively during the administration of clevidipine. Demographic data included age, weight, gender, type of CHD, and surgical procedure performed. Clevidipine was used to control perioperative hypertension defined as systolic BP greater than 95% for age.

Information regarding clevidipine included the initial infusion rate, time to achieve the target BP, the maintenance infusion rate, the average infusion rate, and the duration of administration. Hemodynamic information included the initial BP or mean arterial pressure (MAP) and heart rate (HR) as well as the MAP and HR during the clevidipine infusion. The medical records were also reviewed for adverse effects related to clevidipine including excessive hypotension (need to discontinue the infusion or the need for administration of a fluid bolus and/or vasopressor) and tachycardia (HR increase ≥ 20 beats per minute or need for the administration of a β -adrenergic antagonist). The data are presented as the mean \pm SD. The HR and MAP before and after bolus dosing of clevidipine were compared using a paired *t* test.

RESULTS

The study cohort included 14 patients who ranged in age from 11 months to 15 years (7.2 ± 4.6 years) and in weight from 5 to 45 kg (24.1 ± 13.1 kg). There were 7 males and 7 females. Clevidipine was administered in one of 3 scenarios: 1) as a continuous infusion to control postoperative BP ($n=6$), 2) as a continuous infusion for intraoperative control of MAP during cooling and cardiopulmonary bypass (CPB) ($n=3$), or 3) as a bolus dose for the treatment of hypertension during emergence from anesthesia ($n=5$). The demographic data and surgical procedures are listed in the Table. Clevidipine was used for postoperative BP control in 6 patients, including 3 patients following repair of aortic coarctation. The infusion was started at 1 mcg/kg/min and increased in increments of 0.5 to 1 mcg/kg/min every 2 to 3 minutes as needed. In these 6 patients, the dosing requirements varied from 1 to 7 mcg/kg/min (2.0 ± 1.2 mcg/kg/min). The target BP was reached within 5 minutes in all 6 patients. The duration of the postoperative infusion varied from 8 to 19 hours (13.9 ± 5.1 hours). Two patients were treated with either intravenous or oral propranolol for a HR increase ≥ 20 beats/minute from baseline while receiving clevidipine. These 2 patients required the larger end of the dosing range (5–7 mcg/kg/min) for effective postoperative BP control (1 following repair of aortic coarctation and 1 following aortic valve replacement). All 6 of these patients were weaned off clevidipine with 4 being transitioned to oral therapy with either propranolol or captopril.

Clevidipine was administered intraoperatively as a continuous infusion to control MAP during cooling (core body temperature of 28°C–32°C) while on CPB in 3 patients. Despite doses up to 10 mcg/kg/min, effective control of MAP could not be achieved in any patient. Therapy was switched to either sodium nitropruside or phentolamine, which effectively controlled MAP during CPB.

Clevidipine was administered by bolus doses to 5 patients to control BP during emergence from anesthesia prior to tracheal extubation in the operating room for fast-track anesthesia. A total of 9 bolus doses, ranging from 10 to 15 mcg/kg, were administered to these 5 patients. Two bolus doses were administered to 4 of the patients while 1 patient received 1 bolus dose. Following the 9 bolus doses, MAP decreased from 97 ± 6 mm Hg to 71 ± 5 mm Hg ($p<0.01$). The percent decrease of the MAP from baseline averaged 27% with a range of 22% to 37%. Following the bolus dosing, HR increased by 10 ± 4 beats/minute ($p<0.01$). In 1 patient, the HR increase was ≥ 20 beats/minute following one of the boluses but no treatment was

Table. Demographic Data of the Study Cohort

Patient No. (Sex)	Age, (yr)	Weight, (kg)	Cardiac defect – procedure	Clevidipine dosing (average infusion rate; dosing range)
1(F)	1.5	11	Repair of aortic coarctation	4.3 mcg/kg/min* (1–7 mcg/kg/min) [†]
2(M)	7	20	Repair of aortic coarctation	2 mcg/kg/min* (1–6 mcg/kg/min) [†]
3(M)	0.92	5.8	Repair of aortic coarctation	1.2 mcg/kg/min* (1–4 mcg/kg/min) [†]
4(M)	14	41	Repair of TOF	1.5 mcg/kg/min* (1–3 mcg/kg/min) [†]
5(F)	5	19	Repair of TOF	1.5 mcg/kg/min* (1–2 mcg/kg/min) [†]
6(M)	15	37	Aortic valve replacement for aortic stenosis	1.5 mcg/kg/min* (1–3 mcg/kg/min) [†]
7(F)	6	20	Repair of TOF	Dose up to 10 mcg/kg/min was ineffective in lowering MAP during cooling and CPB.
8(F)	5	19	Repair of TOF	Dose up to 10 mcg/kg/min was ineffective in lowering MAP during cooling and CPB.
9(M)	4	17	ASD and VSD	Dose up to 10 mcg/kg/min was ineffective in lowering MAP during cooling and CPB.
10(F)	5	14	VSD	10–15 mcg/kg for 2 doses [‡]
11(F)	13	45	ASD	10–15 mcg/kg for 2 doses [‡]
12(M)	8	31	ASD	10–15 mcg/kg for 2 doses [‡]
13(F)	12	45	ASD	10–15 mcg/kg for 1 doses [‡]
14(M)	4	13	Repair of PAPVR	10–15 mcg/kg for 2 doses [‡]

ASD, atrial septal defect; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; PAPVR, partial anomalous pulmonary venous return; TOF, tetralogy of fallot; VSD, ventricular septal defect

* Average continuous infusion rate

[†] Dosing range of continuous infusion rate

[‡] Bolus dosing

necessary. Other than this mild increase in HR, no other adverse effects were observed during clevidipine administration. The infusion was not discontinued or decreased due to excessive hypotension.

DISCUSSION

Clevidipine, like nicardipine, is an intravenous calcium channel antagonist of the dihydropyridine class that results primarily in vasodilatation of the arterial bed.⁷ Its unique quality is its metabolism by nonspecific blood and tissue esterases, which results in a half-life of 1 to 3 minutes thereby allowing easy titration by continuous intravenous

administration. To date, most experience with this novel calcium channel antagonist has been in the control of perioperative hypertension in the adult population.

In adult cardiac surgical patients, Levy et al⁸ prospectively compared clevidipine with placebo for the control of preoperative hypertension, defined as a systolic BP \geq 140 mm Hg. A clevidipine infusion ranging from 0.4 mcg/kg/min up to a maximum of 8 mcg/kg/min effectively controlled BP (defined as a reduction of systolic BP by \geq 15%) in 92.5% of patients compared with 17.3% of placebo patients (failure rate of 82.7% in placebo-treated patients). The median time to effective BP control was 6 minutes (95% confidence interval, 6–8 minutes). A

mild increase in HR was noted from a preinfusion value of 71 beats/minute to a maximum value of 84 beats/minute. There were no differences between clevidipine and placebo regarding the adverse effect profile.

The ESCAPE-2 trial compared clevidipine with placebo in the treatment of postoperative hypertension in adult cardiac surgical patients.⁹ Postoperative hypertension, defined as a systolic BP \geq 140 mm Hg, was treated with either placebo or clevidipine (0.4–8 mcg/kg/min). The goal, defined as a \geq 15% reduction of the systolic BP, was achieved in 91.8% of the patients receiving clevidipine versus 20.4% with placebo ($p < 0.0001$). The median time to achieve BP control was 5.3 minutes (95% confidence interval, 4–7 minutes) following the start of the clevidipine infusion. No statistically significant change in HR occurred.

When compared with other antihypertensive agents, preliminary data also support the efficacy of clevidipine. Aronson et al¹⁰ prospectively compared clevidipine with sodium nitroprusside, nitroglycerin, or nicardipine for the treatment of acute hypertension in adult cardiac surgery patients. BP control was more effective with clevidipine when compared with nitroglycerin ($p = 0.0006$) or sodium nitroprusside ($p = 0.003$) but was no different than control with nicardipine. Mortality was lower in patients receiving clevidipine than patients receiving sodium nitroprusside ($p = 0.04$).

In the only published data regarding pediatric use of clevidipine, Towe and Tobias⁶ demonstrated the efficacy of clevidipine in a cohort of 10 pediatric patients who ranged in age from 9 to 18 years. Clevidipine was used preoperatively, intraoperatively, and postoperatively in doses ranging from 0.5 to 3.5 mcg/kg/min. The clevidipine infusion was initiated at 0.5 mcg/kg/min in 8 patients and at 1 mcg/kg/min in the other 2 patients and then titrated up in increments of 0.5 mcg/kg/min every 3 to 5 minutes to achieve effective BP control. The higher end of the dosing range was needed for the induction of controlled hypotension during spinal surgery. Two of the 10 patients required intermittent doses of metoprolol to control an associated increase in HR. No adverse effects such as excessive hypotension were noted. As clevidipine is administered in a lipid emulsion, triglyceride levels were obtained in 3 patients who received clevidipine with propofol. The triglyceride value was elevated (328 mg/dL, normal values 50–150 mg/dL) in 1 patient following the prolonged (4–6 hour) administration of propofol at doses of 50 to 100 mcg/kg/min and clevidipine at 2 to 3.5 mcg/kg/min.

Several agents have been used to control perioperative BP in infants and children including sodium nitroprusside, β -adrenergic antagonists,

calcium channel antagonists, and inhibitors of the renin-angiotensin system.^{2,3} Potential problems with sodium nitroprusside include excessive hypotension even when used within recommended dosing guidelines or even cardiovascular collapse with overdosing. The risk of excessive hypotension as well as wide fluctuations in BP mandates intra-arterial BP monitoring. Labetolol is a competitive antagonist of the α_1 -, β_1 -, and β_2 -adrenergic receptors. With the intravenous administration of labetalol, the initial effects on BP occur within 2 to 5 minutes with a peak effect at 5 to 15 minutes. Potential issues include a relatively prolonged duration of action of 2 to 4 hours and an adverse effect profile that includes bradycardia, heart block, depressed left ventricular function, and bronchospasm.

Several case series have demonstrated that nicardipine is an effective agent for the control of BP in infants and children in various clinical scenarios including the perioperative period.⁷ Although the risk of excessive hypotension is limited, its duration of action may be prolonged following a continuous infusion.^{7,11} As clevidipine shares many of the beneficial physiologic effects of nicardipine with a much more predictable and shorter duration of action, it may be advantageous in situations in which the rapid and tight control of BP is required such as the postoperative period following surgery for CHD. In particular, the rapid resolution of its effects following discontinuation of the infusion may be beneficial in situations in which excessive hypotension may be particularly deleterious.

In our cohort of 14 pediatric patients with CHD, clevidipine effectively controlled BP in 2 scenarios including its use by continuous infusion for postoperative hypertension and its administration by bolus dose for emergence hypertension during fast-track cardiac anesthesia. Although there are no previous reports regarding bolus dosing of this rapidly acting agent, such a use may be considered when the stimulus causing BP elevation is expected to short-lived such as the presence of an endotracheal tube during emergence from anesthesia. In our experience, bolus dosing of 10 to 15 mcg/kg was effective in rapidly controlling hypertension during emergence from anesthesia and was well tolerated without excessive hypotension.

Clevidipine was not effective in controlling MAP during cooling while on CPB even when used in doses up to 10 mcg/kg/min. During cooling while on CPB, vasoconstriction may occur resulting in an increase in MAP. In this scenario, direct-acting vasodilators may be used to decrease MAP. To date, there are limited data regarding the use of calcium channel antagonists in this scenario. We

would speculate that the failure of clevidipine during hypothermia may relate to the inactivation of calcium channels during this degree of hypothermia. The mechanisms responsible for what we observed do not appear to pertain to other pharmacologic agents, such as phentolamine and sodium nitroprusside, whose actions are dependent on other receptor systems as both were effective in controlling the MAP during hypothermia. Alternative possibilities to explain why clevidipine was ineffective during hypothermia include an alteration in the efficiency of binding of the drug to the calcium channel or alterations in the pharmacokinetics of clevidipine. The latter is less likely as clinical experience with other agents that are metabolized by enzymes of the esterase class have demonstrated decreased metabolism and the potential for an increased plasma concentration during hypothermia.¹²

Clevidipine is supplied in a concentration of 0.5 mg/mL in 50- or 100-mL vials. Because of solubility issues, it is provided in a lipid solution and is contraindicated in patients with allergy to eggs, egg products, soy beans, or soy products as well as in patients with disorders of lipid metabolism. Our previous experience has demonstrated the potential for a transient increase in serum triglyceride levels when clevidipine is administered with propofol.⁶ However, no elevation of serum triglyceride level has been noted in adult patients when clevidipine is used alone. In addition, the phospholipids of the solution support bacterial growth so vials of this product are single-use and should not be used for more than 4 to 6 hours.

The youngest patient in our current cohort was 11 months of age. Although nicardipine has been used safely in the neonatal population and has been shown to have limited effects on myocardial contractility,^{12,13} given the catastrophic effects of other calcium channel antagonists such as verapamil in neonates and infants,¹⁴ caution is suggested when using clevidipine in this age group until additional data regarding its effects on myocardial contractility are available. Given its efficacy in the adult cardiac population, its pharmacokinetic profile, and the preliminary successes in the pediatric-aged patient, future trials in various clinical scenarios in the pediatric population are warranted.

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