Original Article

Comparing the Efficacy of Nidepine and Cardepine in Lowering Blood Pressure after Cardio-Aortic Surgery: A Randomized, Double-Blinded Controlled Trial

Ekkarat P, MD[1], Sangkhathat S, MD, PhD[2], Namchaisiri J, MD[3]

[1] Department of Surgery, Nakhon Pathom Hospital, Nakhon Pathom, Thailand

[2] Department of Surgery, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

[3] Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Background: Parenteral nicardipine is an effective calcium channel blocker for blood pressure control during the post-cardioaortic surgical period.

Objective: To compare two preparations of nicardipine hydrochloride, Nidepine, and Cardepine, as a single treatment for acute hypertension after cardioaortic surgery in adult patients.

Materials and Methods: The study was a prospective randomized double-blinded controlled trial of 50 post-cardioaortic surgery patients with a systolic pressure greater than 140 mmHg that were divided into two groups. The first group received Nidepine at the initial dose of 1 mg per hour and titrated every 15 minutes until reaching the target blood pressure, while the other group received Cardepine at the same dose. The primary outcome was blood pressure reduction at 15 and 30 minutes of treatment.

Results: The blood pressures in both groups were significantly reduced within 15 minutes with 40% of the cases reaching the target of systolic pressure lower than 140 mmHg at 30 minutes. Systolic pressure reduction at 15 minutes in the Nidepine group (7.45% of baseline) was not significantly different from that of the Cardepine (5.04% of baseline) group. The mean arterial pressure reductions in both groups (6.42% and 6.99% of baseline in the Nidepine group and Cardepine groups, respectively) were comparable. There were no significant differences in total drug use in 24 hours (16.3 and 23.8 mg, respectively). The average duration of therapy was 22.8 hours in the Nidepine group, and 25.3 hours in the Cardepine group. Resumption of medication after cessation of treatment was required in two cases (8%) in the Nidepine group and three cases (12%) in the Cardepine group. There were no statistically significant differences between the groups in overall complication rates.

Conclusion: Nidepine is therapeutically equivalent to Cardepine in lowering blood pressure in acute hypertension following cardioaortic surgery.

Trial registration: Thai Clinical Trials Registry, TCTR20190206003

Keywords: Hypertension, Cardiac surgery, Calcium channel blocker, Nicardepine

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Hypertension during the immediate post-operative hours is a common condition following a cardio-aortic surgery, reported in 15% to 40% of cases with the highest incidence in coronary artery bypass graft (CABG)[1]. Although the majority of the cases can be explained by various factors including physiologic response to pain or hypercarbia, inadequate sedation, increased volume mobilization into the intravascular space, or pre-existing hypertension, it has been estimated that around 15% of post-operative hypertension cases have no specific cause[2,3]. In patients who undergo CABG surgery, the hypertensive event is known as "post coronary bypass hypertension" and is suspected to be secondary to a transient impairment of the autonomic nervous system

Correspondence to:

Namchaisiri J.

Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Phone: +66-2-2564117, **Fax**: +66-2-2564194

Email: n_jule@hotmail.com

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after a cardiopulmonary bypass[4,5]. Post-cardiac surgical hypertension may have deleterious effects on the vascular anastomosis, cause damage to the vascular graft, or lead to cerebrovascular accidents[6]. In addition, an increased afterload caused by systemic hypertension results in increased metabolic demand of the recovering myocardium and depressed ventricular performance[7]. Intensive blood pressure monitoring and appropriate use of antihypertensive drugs is mandatory in all post-cardioaortic surgery patients. Adequate control of perioperative blood pressure has been found to lead to decreased length of stay and hospital costs in cardiac surgery patients[8,9].

Various titratable short-acting antihypertensive agents are used in immediate post-cardio-aortic surgery period such as sodium nitroprusside, nitroglycerine, beta-blockers, and calcium channel blockers (CCB). Nicardipine, a dihydropyridine CCB with selective effect on peripheral vascular smooth muscle, has long been used in blood pressure control after cardiac surgery[10,11]. Studies have shown superior efficacy of CCBs in lowering both systemic pressure and mean pulmonary pressure[12]. According to the ECLIPSE trial, a rapid acting dihydropyridine CCB was shown to have higher efficacy in maintaining blood pressure when compared with nitroglycerine and sodium nitroprusside and equivalent efficacy with conventional dihydropyridine CCBs[13]. Apart from blood pressure reduction by means of reducing vascular tone, CCB has been shown to reduce myocardial ischemia in a post-cardiac surgery setting[14].

In Thailand, there are several preparations of nicardipine hydrochloride registered with the National Drug Information Registry. However, the original Cardepine Injection (manufactured in the Philippines under license from Astellas Pharma Inc., Japan) is the only preparation available in our hospital drug list that has been approved to be used in daily practice[15]. Among the registered preparations, Nidepine (product of Universal Medical Industry, Thailand), is the only locally manufactured parenteral nicardipine hydrochloride product available in Thai market, and it features both lower cost and equivalent pharmacokinetics to the others. The present study aimed to compare the clinical efficacy of two preparations of nicardipine, Nidepine, and Cardepine in lowering blood pressure for patients with post-operative hypertension after cardioaortic surgery.

Materials and Methods

The study was a prospective randomized double-blinded controlled trial carried in the cardiovascular thoracic intensive care unit of Chulalongkorn Memorial Hospital, Thailand between October 2017 and November 2018. Patients aged more than 18-years-old that underwent a cardiac or an aortic arch surgery were enrolled and continuously observed for blood pressure during their admission in the intensive care unit. Those with post-operative hypertension, defined as systolic blood pressure (SBP) of more than 140 mmHg, who required acute treatment and met no exclusion criteria were randomized into two groups, group A receiving Cardepine and group B receiving Nidepine in the same dosage. By sample size calculation for non-inferiority in the blood pressure lowering efficacy of Nidepine, the number of participants in each arm was set at 25. The study was approved by the Institutional Review Board Office, Research Affairs, Faculty of Medicine, Chulalongkorn University.

Patients were invited to be enrolled into the study before their surgery. Inclusion criteria for randomization were patients who underwent any cardiac procedures or aortic arch procedures including endovascular surgery and had post-operative elevation of SBP at more than 140 mmHg within the first 24 hours post-surgery despite of adequate analgesic or sedative management. Patients were excluded from the study if there were supine heart rate greater than 150 beats per minute or supraventricular tachycardia during the immediate post-operative period, sternal drain output of more than 200 ml in the first hour, hypercarbia (partial pressure of carbon dioxide (pCO_2) of more than 40 mmHg), clinically significant hepatic disease, recent cerebrovascular accident within the past three months, allergic or intolerant to CCB, or pregnancy.

Randomization was performed using computer-generated block randomization. Only the pharmacist knew the label of each CCB preparation used in each case. The drugs were prepared at the pharmaceutical department of the study institution by diluting the studied preparation with 0.9% saline solution to obtain solutions having the concentration of 0.2 mg per ml. The nurses and surgeons involved in the study were blinded to the label until the end of the study period, or if a patient developed high blood pressure that could not be controlled despite using the maximum dose. For safety reasons, a preliminary analysis was performed when complete data from the first 14 cases had been collected. In all patients, the CCB was administered via a central venous catheter under control of an infusion pump. During the initial 15 minutes, all patients received either Cardepine or Nidepine at the

rate of 1 mg per hour. After 15 minutes, the dose was titrated to achieve the target blood pressure by doctors in charge at increments of 0.5 to 1 mg per hour, every 15 to 20 minutes. During the study period, there were no other combined parenteral antihypertensive drugs infused together with the CCB, except for the intravenous fentanyl (1 microgram per kilogram per hour) for the purpose of pain control. If the maximum dose of 15 mg per hour was ineffective in lowering the blood pressure, the pharmacists would be contacted for label disclosure. If the patient was in the Nidepine group, the drug would be switched to Cardepine and adjuvant antihypertensive agents considered.

The primary outcome was mean arterial blood pressure reduction at 15 and 30 minutes of therapy. Total drug used and complications were also analyzed. Vital signs were measured every 15 minutes in the first hour of treatment and then every 30 to 60 minutes until cessation of the therapy, which was defined as the time the antihypertensive drug was switched to oral form or discharge from the intensive care unit. Continuous data are presented as mean and standard deviation or median and interquartile range as appropriate. Comparisons of data used the 2-sample t-test or non-parametric Mann-Whitney U test. The statistical package Stata Release 13.0 (StataCorp LP, College Station, TX, USA) was used for analysis.

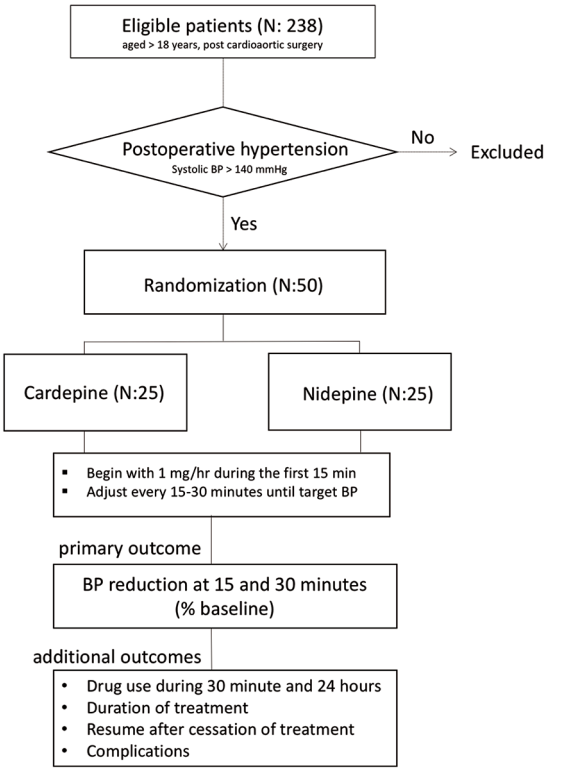

Figure 1. Schematic representation of the study design.
BP: blood pressure

Results

During the study period, 233 patients underwent cardioaortic surgery and consented to be eligible to participate the study. Among those, 50 cases met the inclusion criteria and were randomized (Figure 1). Most of the patients were diagnosed as coronary artery disease. There were no statistically significant differences in baseline characteristics between the two groups (Table 1). Most of the patients underwent CABG operation (Table 2). Unintentionally, the Cardepine group had more cardiac transplantation cases, although not at the level of statistical significance. The average intensive care stays in the Cardepine group (76 hours) was higher than in that of the Nidepine group with borderline statistical significance (53 hours, p=0.05).

In both groups, the average systolic and diastolic blood pressures (DBP) were significantly reduced from baseline at 15 minutes of drug administration (Table 3). At 30 minutes, 11 cases in the Cardepine group (44%) and nine cases in the Nidepine group (36%) had achieved the SBP goal of 140 mmHg or less (p=0.56). Considering the diastolic pressure at 30 minutes, 17 cases (68%) in the Cardepine group and 20 cases (80%) in the Nidepine group were at less than 80 mmHg (p=0.33) (Figure 2). In the Cardepine group, the average SBP had fallen from 165.6 mmHg to 156.8 mmHg at 15 minutes and then to 148.4 mmHg at 30 minutes (p<0.01), while the DBP fell from 87.8 mmHg to 79.8 mmHg at 15 minutes and to 74.0 mmHg at 30 minutes (p<0.01). In the Nidepine group, the average SBP fell from 178.8 mmHg to 164.9 mmHg at 15 minutes and to 148.6 mmHg at 30 minutes (p<0.01), while the DBP fell from 82.0 mmHg to 78.8 mmHg at 15 minutes and 71.6 mmHg at 30 minutes (p<0.01). The reductions in mean arterial pressure (MAP) are diagrammed in the Figure 3. There were no statistically significant differences in percentage reductions of blood pressure between the groups although reduction of SBP in the first 15 minutes seemed to be higher in the Nidepine group while reduction of DBP seemed higher in the Cardepine group.

The average drug dosages had no statistically significant differences between the two groups. After the therapy, intravenous CCB was resumed in five patients (10.0%), three in the Cardepine group and two in the Nidepine group (p=1.00). Seven cases had complications during the treatment and included

Table 1. Comparing baseline pre-operative data between the study groups

Parameters	Cardepine (n=25)	Nidepine (n=25)	p-value
Sex			1.00
Male	14 (56.0%)	14 (56.0%)	
Female	11 (44.0%)	11 (44.0%)	
Age (years)	58.2	64.5	0.12
Body weight (kg)	63.1	60.1	0.69
BMI (kg/m^2)	23.9	25.1	0.57
Diagnosis			
Valvular heart diseases	9	6	0.35
Aortic aneurysm	4	7	0.31
Coronary artery disease/ others	12	12	1.00
Underlying diseases			
Hypertension	18	19	0.75
Diabetes mellitus	5	10	0.12
End staged renal disease	2	3	0.64
Dyslipidemia	9	9	1.00
Gouty arthritis	2	1	0.55
No underlying disease	5	2	0.22
Pre-operative medication use			
Beta-blocker	15	15	1.00
Calcium channel blocker	8	10	0.56
Diuretic	9	7	0.54
ACEI	13	10	0.39
Vasodilator	8	4	0.19
Baseline pre-operative data			
Systolic blood pressure (mmHg)	131.9	135.4	0.56
Diastolic (mmHg)	73.7	72.4	0.69
Heart rate (beats/minute)	75.8	77.4	0.65
Ejection fraction (%)	52.8	55.0	0.60
Hemoglobin (g/dL)	11.9	11.2	0.27
Serum albumin (g/dL)	3.9	3.8	0.62
Creatinine (mg/dL)	1.19	1.82	0.10

ACEI=angiotensin converting enzyme inhibitor; BMI=body mass index

Table 2. Comparing operative data between the 2 nicardipine groups

Parameters	Cardepine	Nidepine	p-value
Operation			
Valve replacement	6	7	0.74
Coronary artery bypass graft	10	11	0.77
Open/endovascular procedures	7	7	1.00
Cardiac transplantation	3	0	0.07
Operative duration (minutes)	272	253	0.55
Cardiopulmonary bypass duration (minutes)	147	123	0.28
Aortic clamp time (minutes)	114	101	0.53
Intubation duration (hours)	18	15	0.59
Intensive care unit stay (hours)	76	53	0.05

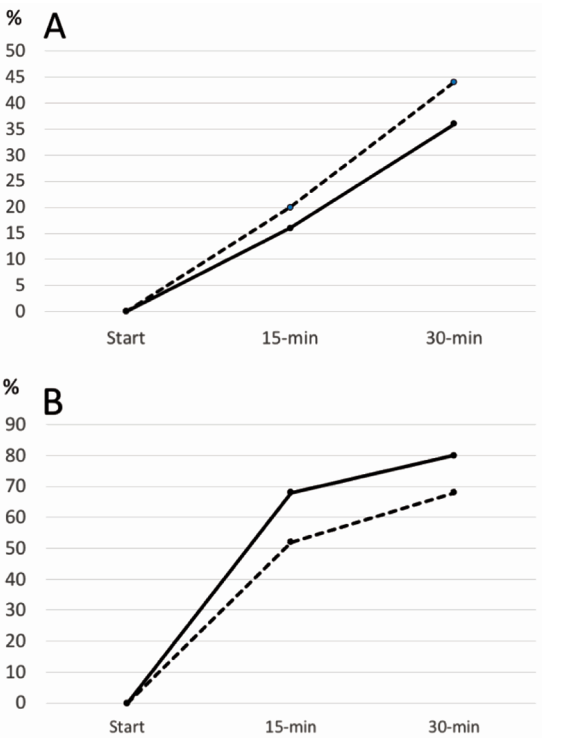

Figure 2. Percentage of cases whose (A) systolic blood pressure reached the target of less than 140 mmHg, (B) diastolic blood pressure less than 80 mmHg at 15 minutes and 30 minutes of drug initiation. Solid line showed Nidepine group; Dotted line showed Cardepine group.

three in the Cardepine group and four in the Nidepine group (p=0.16). There were no mortalities in the study (Table 3).

Discussion

CCB is an effective drug for lowering blood pressure in the condition of acute hypertensive episode following cardio-aortic surgery[11]. Consistent with an earlier report, the present study showed significant reduction of MAP of at least 5% of baseline within 15 to 30 minutes of initiation of therapy in both the original Cardepine drug group and the generic nicardepine group with identical active ingredients[12]. Blood pressure raised after discontinuation of the drugs in five patients, two in the Nidepine group which

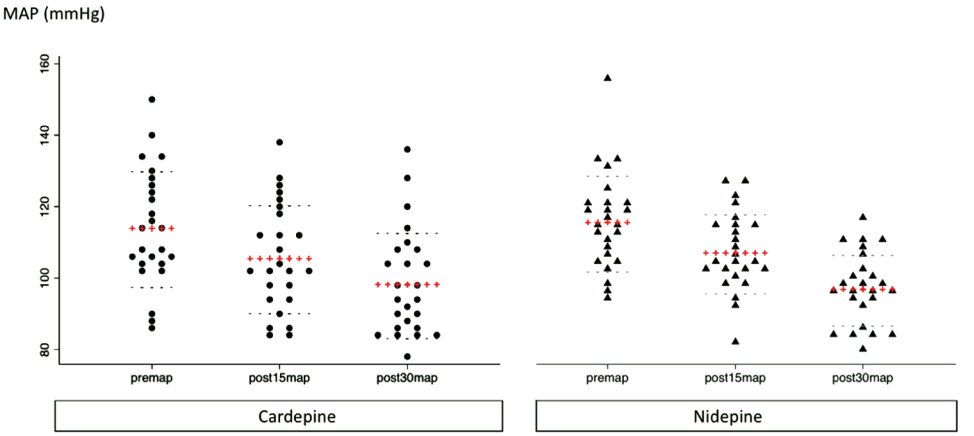

Figure 3. Scatter plots showing changes in mean arterial pressure measured at 15 and 30 minutes of nicardipine treatment. The red lines showed the average values of each point while the upper and the lower lines showed standard deviations.

Table 3. Outcomes comparisons between the 2 groups

Parameters	Cardepine	Nicardepine	p-value
Therapeutic effect at 15 minutes			
SBP reduction at 15 minutes (% of baseline)	5.04	7.45	0.32
DBP reduction at 15 minutes (% of baseline)	6.64	2.46	0.21
MAP reduction at 15 minutes (% of baseline)	6.99	6.42	0.83
Therapeutic effect at 30 minutes			
SBP reduction at 30 minutes (% of baseline)	5.27	9.09	0.16
DBP reduction at 30 minutes (% of baseline)	6.87	10.57	0.27
MAP reduction at 30 minutes (% of baseline)	6.58	8.58	0.46
Dosages			
Dosage in the first 30 minutes (mg)	0.65	0.85	0.15
Dosage in the first 24 hours (mg)	23.75	16.30	0.11
Total drug duration (hours)	25.30	22.80	0.70
Adverse outcomes			
Resume after cessation of therapy	3 (12%)	2 (8%)	1.00
Complication during therapy	3 (12%)	4 (16%)	0.16
• Hypotensive complication	2 (8%)	1 (4%)	
• Re-intubation	1 (4%)	2 (8%)	
• Surgical bleeding	0 (0%)	1 (4%)	

SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure

included one patient who became hypertensive after a re-operation, and a patient who became hypertensive during a re-intubation, and three in the Cardepine group which included one who developed high blood pressure during a re-intubation and two without any specific associated event.

The present study found relatively lower dosages and durations needed for blood pressure control with Nidepine when compared to Cardepine, although the differences did not reach statistically significant levels. However, the study was designed to be a non-inferiority trial that compare the decline in blood pressure as a primary outcome and case the number might not be adequate to compare the dosage. Although the active pharmaceutical ingredient of Cardepine and Nidepine, nicardepine hydrochloride, is the same, other inert ingredients could possibly cause some effects as they generally help enhancing

properties of preparation such as buffering system, solubility, pH, or tonicity, etc. Any difference in type or quality could be assumed to cause some differences in properties of preparation. Nicardepine hydrochloride has two optical isomers, a plus form (+ form) and a minus form (– form), and the + isomer has three times more potential for interacting with a calcium channel when compared to the – form[16]. As the racemic mixture of nicardepine hydrochloride is composed of both ± racemic isomers, the difference in a ratio of these two isomers in substances from different sources might possibly lead to difference in pharmacological efficacy.

Conclusion

In conclusion, the present study compared the pharmacodynamics of a generic preparation of nicardepine, Nidepine, against the original drug, Cardepine and found no inferiority in its efficacy in lowering blood pressure in post-cardioaortic surgery patients. In addition, there were no differences in the adverse events between the two drugs.

What is already known on this topic?

Nicardepine hydrochloride is an effective blood pressure control agent that can be used in various post-operative setting, including post-cardioaortic surgery.

What this study adds?

Apart from the Cardepine, which is an original drug, a generic preparation of nicardepine hydrochloride, Nidepine has similar efficacy in acute blood pressure lowering during an immediate post-operative period in cardioaortic surgery.

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Dave Patterson of the Office of International Affair, Faculty of Medicine, Prince of Songkla University edited the English Language in the manuscript.

Ethical approval and consent to participate

The study has been approved by the Institutional Review Board Office, Research Affairs, Faculty of Medicine, Chulalongkorn University (COA No.704/2017).

Consent for publication

The corresponding author (Namchaisiri J) submitted the manuscript on behalf of all authors who have been informed and have agreed with this submission.

Availability of supporting data

All relevant data of the study is shown in the manuscript. There is no additional supporting data.

Authors' contributions

Ekkarat P was the principal investigator who designed, conducted the study and draft the manuscript. Namchaisiri J supervised the study and provided clinical information of the patients. Sangkhathat S performed data management and manuscript editing.

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Conflicts of interest

The authors declare no conflict of interest.

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