

Title: NICARDIPINE VS. PLACEBO FOR THE TREATMENT OF POSTOPERATIVE HYPERTENSION

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**Introduction:** Nicardipine is a new intravenous dihydropyridine calcium channel antagonist with significant vasodilating properties.<sup>1</sup> The elimination half life of nicardipine is 1-5 hrs which allows administration as a constant infusion which can be titrated to the desired effect.<sup>2</sup> This multicenter, double blinded, randomized study was designed to evaluate the antihypertensive efficacy of IV nicardipine in comparison to placebo in the postoperative period.

**Methods:** One hundred thirteen patients with postoperative hypertension who gave informed consent were entered into this institutional review board approved study. After surgery and prior to treatment, baseline blood pressure (BP) and heart rate (HR) measurements were obtained and the patients assigned to receive IV nicardipine or placebo treatment in a 3:2 ratio. Postoperative hypertension was defined as the average of three consecutive BP measurements, at least two minutes apart not varying by > 15% consisting of systolic (SBP)  $\geq$  140 mmHg or diastolic (DBP)  $\geq$  95 mmHg blood pressures. Study drug was initially infused at a rate of 10 mg/hr for 5 min. If necessary the infusion was increased to 12.5 mg/hr for 5 min and finally to 15.0 mg/hr for 15 min until therapeutic response was achieved (> 15% reduction from entrance SBP or DBP). BP and HR were obtained frequently during the titration period.

Once therapeutic response occurred, maintenance infusion was initiated at 3 mg/hr for 15 min. If needed, the infusion was adjusted upward or downward by 1-2.5 mg/hr every 15 min to maintain BP control. Nicardipine was given for up to 8 hrs by peripheral vein and 24 hrs if centrally administered. BP and HR measurements during the maintenance period were taken at periodic intervals until the infusion was discontinued. In the patients with inadequate rate of BP reduction or  $\geq$  15% decrease in BP at 15.0 mg/hr for 15 min, the blinding code was opened. If these patients were receiving placebo, open label IV nicardipine or an alternate antihypertensive agent was administered. Those patients who were initially treated with nicardipine but did not respond were given an alternate medication. Once the study medication was discontinued, the patients were monitored until 1) there was a 10 mmHg rise in BP over the last BP of the infusion period; 2) alternate therapy was started, or 3) 24 hr had elapsed.

**Results:** Analysis of safety data was conducted in all 113 patients, whereas results for preliminary efficacy analysis were available for 79 patients. There was no significant difference in demographics between the nicardipine and placebo groups. Forty-four of 47 (94%) patients achieved therapeutic response with IV nicardipine treatment compared to 3/32 (9%) with placebo treatment ( $p < 0.001$ ) (Fig I). One responder to nicardipine was discontinued after

the titration period due to hypotension. Twenty-three of 29 non-responders to placebo were subsequently given IV nicardipine. Eighty-seven percent of these patients (20/23) responded to open label nicardipine. There was a slight but insignificant increase in heart rate (Table I) seen with nicardipine treatment. Frequently reported side effects include nausea and/or vomiting ( $n=5$ , 4%) and hypotension ( $n=6$ , 5%). The incidence of all side effects was 17% (19/113), however, none of these events was deemed clinically significant. The time to BP control for nicardipine responders was rapid with 13/44 achieving response in 5 min (at 10 mg/hr), 15/44 in 10 min (at 12.5 mg/hr) and 16/44 during the 15 min titration at 15 mg/hr. Eight patients required maintenance infusion for < 2 hrs, 8 for 3-5 hr, 24 for 6-10 hr and 3 required maintenance for > 15 hr.

**Discussion:** Our results indicate that nicardipine is an effective medication to treat postoperative hypertension. This confirms previous findings in unblinded trials.<sup>3</sup> Nicardipine has powerful coronary vasodilating properties which improve tolerance to pacing induced ischemia.<sup>4</sup> The combination of systemic vasodilation, coronary vasodilation and minimal effect on heart rate make nicardipine a valuable antihypertensive agent for the treatment of postoperative hypertension.

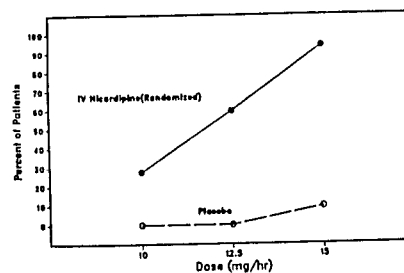


Figure I  
% of patients achieving therapeutic response

Table I (mean  $\pm$  SD) Hemodynamic Variable

		Baseline	N	End of		N
				Titration	Maintenance	
SBP	Nic	179.9 $\pm$ 21.2	47	143.1 $\pm$ 21.8*	47	133.9 $\pm$ 20.4
	Plac	174.2 $\pm$ 20.6	32	169.0 $\pm$ 24.7*	32	101.0 $\pm$ 5.7
DBP	Nic	93.9 $\pm$ 12.9	46	75.3 $\pm$ 12.8*	47	73.1 $\pm$ 7.7
	Plac	94.2 $\pm$ 10.7	32	92.7 $\pm$ 14.6*	32	67.5 $\pm$ 10.6
HR	Nic	81.4 $\pm$ 15.8	47	85.9 $\pm$ 16.2	47	86.5 $\pm$ 15.8
	Plac	84.4 $\pm$ 13.8	32	85.1 $\pm$ 14.3	32	78.0 $\pm$ 28.3

\* $p < 0.001$  placebo vs nicardipine

References

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