Anesthesiology
71:835–839, 1989

Intravenous Labetalol Versus *Sodium Nitroprusside for Treatment of Hypertension Postcoronary Bypass Surgery*

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Hypertension is common following coronary artery bypass surgery. The safety of labetalol, a recently released combined α_1 and β-adrenergic blocking agent for treatment of hypertension in this clinical situation is controversial. The authors compared the hemodynamic effects of labetalol with those of sodium nitroprusside (SNP) in 91 patients with good left ventricular function and equally severe coronary artery disease and in whom coronary artery bypass surgery had been just completed. They were anesthetized using fentanyl, diazepam, and enflurane. If hypertension developed postoperatively, patients were randomized to receive labetalol, 2 mg/min to a maximum of 300 mg (20 patients) or sodium nitroprusside in 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increments by infusion (20 patients) to return blood pressure to normal. Compared with control values, labetalol brought about significant ($P < 0.05$) reductions in heart rate, and cardiac index. No change was noted in stroke volume or systemic vascular resistance, but slight increases were found in central venous pressure and pulmonary capillary wedge pressure. Sodium nitroprusside treatment caused significant increases in heart rate and cardiac index while reducing diastolic blood pressure, central venous pressure, and pulmonary capillary wedge pressure. Stroke volume remained unchanged. Following the study period, blood pressure was controlled in all patients with SNP. Total doses of SNP in the 16 h following the study period were significantly less in the labetalol group (46.6 ± 11.7 mg) *versus* (116.1 ± 10.3 mg) in the SNP group ($P < 0.05$). In this clinical circumstance, labetalol can be safe and effective for controlling hypertension, but its mechanism of achieving this effect varies from that for sodium nitroprusside. Labetalol may improve myocardial oxygen balance and allow for reduced cumulative doses of sodium nitroprusside in this clinical setting. (Key words: Anesthetic techniques, hypotensive: nitroprusside; labetalol. Blood pressure, hypertension: postoperative.)

THIRTY TO FIFTY PERCENT of patients undergoing coronary artery bypass surgery experience postoperative hypertension.[1,2] This may have deleterious consequences, such as bleeding from vascular suture lines or cannulation sites,[3] cerebrovascular hemorrhage, or subendocardial ischemia.[4]

Numerous agents have been shown to be effective in controlling hypertension during the postoperative period. Sodium nitroprusside, owing to its rapid onset, short duration of action, and ease of titration appears to offer some advantages over other agents. It has become a popular choice for the management of hypertension after open heart surgery.[5–7]

Intravenous labetalol, a combined selective α_1 and β-adrenergic blocking agent,[8] has been used extensively as an antihypertensive in a variety of clinical settings,[9] but its safety for blood pressure control in the hypertensive patient following coronary artery bypass grafting (CABG) remains controversial.[10,11] The deleterious effect most often quoted is labetalol's potential negative inotropic effects on the myocardium. Few studies attest to its safety[12,13] and there are no randomized trials comparing labetalol to other treatment modalities in this patient population.

We studied the efficacy of labetalol in decreasing blood pressure in patients following CABG, assessed the drug's safety, and compared its hemodynamic effects to those of sodium nitroprusside.

Methods

Following institutional approval, informed consent was obtained from 91 patients scheduled for elective CABG. All patients eligible for the study were entered sequentially during two 8-week periods. No patients refused to be entered into the study. The inclusion criteria were: 1) ages 40–70 yr; 2) left ventricular ejection fraction (LVEF) greater than 40% at rest (as assessed by preoperative echocardiography, MUGA [MUltiGAted nuclear ventriculography] scan, or contrast ventriculography); 3) no evidence of valvular heart disease; 4) no contraindication to β-adrenergic blocking agents; 5) intraoperative aortic cross-clamp time of less than 90 min; and 6) stable postoperative course (*i.e.*, no difficulty in separation from cardiopulmonary bypass and no dysrythmia or need for inotropic agents).

No attempt was made to influence intraoperative anesthetic and surgical management. All patients received their usual medications, except diuretics, on the day of surgery. They received lorazepam (0.01 to 0.03 mg/kg sublingually) or diazepam (0.11 to 0.21 mg/kg orally) 2 h preoperatively, and morphine (0.11 to 0.23 mg/kg)

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Received from the Departments of Anesthesia and Internal Medicine, and the Division of Cardiovascular Surgery, Department of Surgery, Toronto Western Hospital, Toronto, Ontario, Canada. Accepted for publication July 11, 1989. Presented in part at the Canadian Anaesthestists' Society Annual Meeting. Halifax, Nova Scotia, June 27, 1988. Supported in part by a grant from Glaxo, Canada.

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and perphenazine (0.04 to 0.11 mg/kg) intramuscularly 1 h preoperatively.

All patients had pulmonary artery catheters inserted preoperatively, and were anesthetized using fentanyl (50–100 μg/kg), pancuronium (0.15–0.25 mg/kg), diazepam (0.12–0.40 mg/kg), and enflurane. During cardiopulmonary bypass using a membrane oxygenator, myocardial protection was achieved using cold sanguineous (two parts blood to one part crystalloid) potassium cardioplegia, one liter initially, followed by 300–500 mls every 10–20 min. Systemic hypothermia (to 25°–30° C) was also employed.

Postoperatively, following a 1-h stabilization period in the Intensive Care Unit, antihypertensive therapy (which, if required, consisted solely of sodium nitroprusside) was discontinued, and the blood pressure allowed to increase over a subsequent 30-min period.

If, during this time, the systolic blood pressure (SBP) exceeded 140 mmHg, or the mean arterial pressure (MAP) exceeded 90 mmHg, patients were considered hypertensive and entered the randomized treatment phase of the study. The following hemodynamic measurements were then obtained: SBP (mmHg), MAP (mmHg), diastolic blood pressure (DBP) (mmHg), heart rate (HR) (beats/min), thermal dilution cardiac output (CO) (l/min), cardiac index (CI) ($l \cdot min^{-1} \cdot m^{-2}$), stroke volume (SV) (ml/beat), systemic vascular resistance (SVR) (dyne-sec $\cdot cm^{-5}$), pulmonary capillary wedge pressure (PCWP) (mmHg), and central venous pressure (CVP) (mmHg). Patient temperature and hematocrit were also recorded.

Patients were randomly allocated to one of two treatment groups. Group 1 (20 patients) received sodium nitroprusside (SNP), 50 mg in 250 ml of 5% dextrose in water (D5W) by iv infusion (initial dose 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and adjusted in 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increments). Group 2 (20 patients) received labetalol (200 mg in 200 ml D5W) by iv infusion at 2 mg/min to a maximum of 300 mg; three iv boluses of 25 mg each were also administered, if necessary, during the first 15 min of labetalol treatment, at 5-min intervals, to control blood pressure.

When adequate blood pressure control was achieved (SBP less than 120 mmHg or MAP less than 80 mmHg), hemodynamic measurements were repeated in triplicate, at 10-min intervals. Following this, if hypertension recurred, it was treated with sodium nitroprusside. All patients received colloid during both the stabilization period and the study period. The number of units of plasma and/or packed red blood cells used during this time was recorded.

Total doses of labetalol during the study period, and of sodium nitroprusside during the subsequent 16-h period in each group were recorded.

Patients' antihypertensive medications prior to surgery were divided into five groups: 1) nitrates (nitroglycerine ointment, isosorbide dinitrate, sustained-release or sublingual nitroglycerine); 2) β-adrenergic blocking drugs (propranolol, metoprolol, atenolol, timolol); 3) calcium channel blocking drugs (nifedipine, diltiazem, verapamil); 4) angiotensin converting enzyme inhibitors (captopril); and 5) diuretics (hydrochlorothiazide, furosemide, triamterene, amiloride).

The number of vessels bypassed and their degree of stenosis prior to surgery were compared. For each coronary vessel (left main coronary artery, left anterior descending, circumflex, and right coronary arteries), numbers were empirically assigned corresponding to degree of stenosis: grade 1 signified a stenosis of 50% or less; grade 2, a 51–75% stenosis; grade 3, a 76–90% stenosis; and grade 4, a greater than 91% stenosis. The degrees of stenosis were obtained from the formal angiography report.

The data were analyzed using Students t test, analysis of covariance, repeated measures analysis of covariance, or Fisher's exact test, where appropriate.[14] Statistics with $P < 0.05$ were deemed significant.

Results

Forty of the 91 patients initially enrolled in our study became hypertensive postoperatively. Of these 40 patients, 50% had received SNP during the 1-h stabilization period prior to randomization. 62.5% of the patients who were randomized in the study were known to have had longstanding (>1 year) hypertension. They were equally divided between the two groups.

There were no significant differences between the groups with respect to age, LVEF, preoperative antihypertensive medications, number of vessels bypassed or their degree of stenosis, cross-clamp time, or cumulative doses of anesthetic drugs administered (table 1). No opioids or benzodiazepines were administered during the postoperative study phase. None of the patients required postoperative pacing. There were no differences in postoperative hematocrit, temperature, or number of units of blood products administered between the two groups.

Hemodynamic data showing differences between drug treatment groups, and changes in values over time following drug treatment within each group, are shown in table 2.

None of the hemodynamic data were significantly different before drug treatment. SBP end points were easily achieved with both drugs. DBP was decreased significantly by SNP ($P < 0.005$) but was not changed by labetalol.

Consequently, MAP fell significantly ($P < 0.005$) in both groups, but more so with SNP than labetalol, since between group values differed at each time period ($P < 0.05$).

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TABLE 1. Study Population

Patient Characteristics	Group 1 (Sodium Nitroprusside)	Group 2 (Labetalol)	P†
Number of patients	20	20	
Age (yr)*	58.0 ± 1.7	57.2 ± 1.9	NS
Preoperative LVEF (No. of patients)			
>60%	12	15	
40–60%	8	5	
Intraoperative drug requirements			
Fentanyl (ug/kg)*	86.5 ± 2.9	82.7 ± 3.6	NS
Pancuronium (mg/kg)*	0.18 ± 0.01	0.18 ± 0.01	NS
Diazepam (mg/kg)*	0.21 ± 0.02	0.18 ± 0.01	NS
Cross clamp time (min)*	58.0 ± 3.3	50.6 ± 3.6	NS
Postoperative body temperature (°C)*	34.9 ± 0.15	34.9 ± 0.23	NS
Postoperative hemoglobin (g/l)*	103.4 ± 2.3	102.7 ± 2.6	NS
Units of blood products administered*	3.1 ± 2.2	3.6 ± 2.6	NS

* Mean ± SEM.

† NS no significant difference between groups ($P > 0.05$).

The HR rise with SNP (80.6 ± 3.7–89.3 ± 3.3 beats/min) and decrease with labetalol (85.4 ± 3.1–78.8 ± 1 beats/min) were also significant ($P < 0.005$).

CVP rose from 10.6 ± 0.8 (control) to 13.2 ± 0.7 (30 min) ($P < 0.05$) in the labetalol group, as did PCWP (from 11.8 ± 1.0 [control] to 14.0 ± 0.7 [30 min] [$P < 0.05$]). These same parameters fell in the SNP group (CVP from 9.8 ± 1.0 [control] to 8.8 ± 0.6 [30 min] [$P < 0.05$], and PCWP from 11.5 ± 0.8 [control] to 10.7 ± 0.7 [30 min] [$P < 0.05$]).

TABLE 2. Hemodynamic Variables Related to Drug Therapy*

Hemodynamic Variable	Drug	Control	Time (min) 10	20	30	P†
SBP	SNP	145.5 ± 3.4	121.3 ± 3.3	121.9 ± 2.5	121.3 ± 2.5	<.005
	LAB	150.9 ± 4.3	127.6 ± 4.7	125.7 ± 4.4	120.5 ± 3.8	<.005
	P‡	NS	NS	NS	NS	
DBP	SNP	71.1 ± 2.7	51.2 ± 2.9	49.9 ± 2.8	48.7 ± 2.9	<.005
	LAB	69.6 ± 2.6	67.4 ± 2.4	66.7 ± 2.6	62.5 ± 2.6	NS
	P‡	NS	<.005	<.005	<.005	
MAP	SP	92.8 ± 2.3	71.3 ± 2.8	71.1 ± 2.4	69.2 ± 2.5	<.005
	LAB	92.6 ± 2.6	87.6 ± 2.8	86.1 ± 3.0	80.3 ± 2.8	<.005
	P‡	NS	<.005	<.005	<.05	
HR	SNP	80.6 ± 3.7	85.7 ± 3.7	88.2 ± 3.5	89.3 ± 3.3	<.005
	LAB	85.4 ± 3.1	76.4 ± 1.8	77.3 ± 1.7	78.8 ± 1.6	<.005
	P‡	NS	<.05	<.05	<.05	
CVP	SNP	9.8 ± 1.0	7.9 ± 0.8	8.7 ± 0.7	8.8 ± 0.6	<.05
	LAB	10.6 ± 0.8	12.3 ± 0.8	13.2 ± 0.8	13.2 ± 0.7	<.05
	P‡	NS	<.005	<.005	<.005	
PCWP	SNP	11.5 ± 0.8	9.3 ± 0.4	9.6 ± 0.4	10.7 ± 0.7	<.05
	LAB	11.8 ± 1.0	14.0 ± 0.9	15.0 ± 0.9	14.0 ± 0.7	<.005
	P‡	NS	<.005	<.005	<.005	
CI	SNP	2.9 ± 0.2	3.0 ± 0.2	3.2 ± 0.2	3.4 ± 0.2	NS
	LAB	2.9 ± 0.2	2.4 ± 0.2	2.6 ± 0.2	2.6 ± 0.2	<.05
	P‡	NS	<.05	NS	<.05	
SVR	SNP	1339 ± 130	1032 ± 107	951 ± 89	861 ± 84	<.005
	LAB	1289 ± 129	1369 ± 119	1306 ± 131	1184 ± 112	NS
	P‡	NS	<.05	<.05	<.05	
SV	SNP	66.1 ± 5.6	63.9 ± 5.0	71.2 ± 5.1	75.9 ± 5.4	NS
	LAB	68.7 ± 5.8	65.3 ± 5.2	68.0 ± 6.8	66.0 ± 5.1	NS
	P‡	NS	NS	NS	NS	

SNP = Sodium Nitroprusside. LAB = Labetalol.
* Mean ± SEM.

† Change over time within each group compared with control (RMANOVA).
‡ Change between groups at each time period (*t* test).

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CI increased in the SNP group (from 2.9 ± 0.2 [control] to 3.4 ± 0.2 $l \cdot min^{-1} \cdot m^{-2}$ [30 min]), but this did not achieve statistical significance. With labetalol, CI fell significantly (from 2.9 ± 0.2 [control] to 2.6 ± 0.2 $l \cdot min^{-1} \cdot m^{-2}$ [30 min] [$P < 0.05$]) and was significantly lower than those values during SNP therapy at two time intervals post-treatment (3.0 ± 0.2 *vs* 2.4 ± 0.2 $l \cdot min^{-1} \cdot m^{-2}$ for SNP *vs* labetalol at 10-min post-treatment, and 3.4 ± 0.2 *vs* 2.6 ± 0.2 $l \cdot min^{-1} \cdot m^{-2}$ for SNP *vs* labetalol at 30-min post-treatment, $P < 0.05$).

SVR fell in the SNP group from 1339 ± 130 (control) to 861 ± 84 dynes-sec $\cdot cm^{-5}$ (30 min) ($P = 0.0001$), but did not change in the labetalol group. SV was not significantly different within or between groups at baseline or over time.

The average dose of labetalol was 149.6 ± 15.8 mg/patient. During the 16-h period following randomization, the average dose of SNP was significantly greater in the SNP group compared with that in the labetalol group (116.1 ± 19.3 mg *vs.* 46.6 ± 11.7 mg, $P < 0.05$) (table 3).

TABLE 3. Antihypertensive Therapy

	Group 1 (Sodium Nitroprusside)	Group 2 (Labetalol)
Total labetalol dose (mg)	0	149.6 ± 15.8
Total SNP dose (mg)*	116.1 ± 19.3	46.6 ± 11.7

* Mean ± SE of total dose administered over 16 h following randomization.

Discussion

Forty-four percent of the patients enrolled in our study became hypertensive postoperatively, a finding consistent with previous investigators who quoted a 30–50% incidence.[4]

Hypertension is more likely to occur postoperatively in patients with known, documented hypertension.[11] Of our patients who became hypertensive postoperatively, 62.5% had previously documented hypertension.

Sodium nitroprusside has been used extensively to control postoperative hypertension. Its efficacy in reducing blood pressure in this setting is well reported,[5–7] as is its ability to reduce afterload and preload while preserving cardiac index and ejection fraction. The potential disadvantage of SNP, decreasing coronary perfusion pressure without improving collateral flow, is also well documented.[15–17]

Previous studies on the effect of labetalol on hypertension post-CABG have shown conflicting results. Morel *et al.*[10] administered labetalol to ten normovolemic patients post-CABG, irrespective of preoperative left ventricular ejection fraction (LVEF), which ranged from 30–70% (average 57 ± 12%). Labetalol in doses of less than 140 mg (given in incremental bolus doses from 20–80 mg) was found to be safe and effective. Higher doses caused cardiovascular decompensation resulting in "difficult hemodynamic resuscitation." One patient (whose LVEF was 30%) died.

The effects of labetalol in nine patients with post-CABG hypertension, and in two patients with post-aortic valve replacement (AVR) were examined by Meretoja *et al.*[11] The indications for AVR were not stated. Patients were entered regardless of LV function, and six of the 11 patients had cardiac indices of less than 2.1 $l \cdot min^{-1} \cdot m^{-2}$. Labetalol was given in 1–2 mg increments every 1–2 min. Significant reductions in HR and BP were noted following an average of 15 mg of iv labetalol, with concomitant reductions in CI and little change in SV. Four patients required glucagon infusion for reversal of severe hypotension. These authors concluded that labetalol could not be recommended for the treatment of post-open heart surgery hypertension because of significant reductions in myocardial performance.

Prough *et al.*[12] screened LV function and administered labetalol to seven patients with postoperative SBP of 140 mmHg. They found significantly altered hemodynamics after only 15 mg of labetalol, given in 5-mg, followed by 10-mg, increments. Sladen *et al.*[13] administered labetalol in increasing increments (5, 10, 20, and 40 mg) every 10 min to 48 patients undergoing CABG, whose preoperative LVEF was greater than 40%. Labetalol was found to be safe, and was effective in reducing blood pressure by >10% in 75% of the patients. The majority of the responders (35/48) could be effectively treated with 35 mg or less. They cautioned against the use of the drug in patients with cardiac dysfunction.

Differences in the conclusions about labetalol appear to be attributable to the different populations studied, especially in regards to their left ventricular function, and to the dose and mode of administration of the drug. In our study, only patients with LVEF greater than 40% were selected. In order to avoid the complications associated with administration of large bolus doses of this potentially hemodynamically destabilizing drug, labetalol was given by slow infusion. However, none of the previous studies compared labetalol to a standard therapy for treatment of post-CABG hypertension.

No complications attributable to either drug were noted in our patients. Systolic and mean blood pressure end points were easily achieved with both drugs. These end points were achieved by different means. SNP brought about a reduction in SVR, and maintained CI by an increase in HR and no change in SV. Both CVP and PCWP fell significantly. Labetalol, on the other hand, decreased blood pressure while maintaining SVR. The CI was reduced primarily by reductions in HR, while SV was largely maintained. However, both PCWP and CVP, did increase.

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There was no difference between groups in terms of efficacy of blood pressure control. The lack of deleterious effects (tachycardia, low cardiac output states [CI < 2.0 $l \cdot min^{-1} \cdot m^{-2}$], dysrhythmias, bradycardia requiring drugs and/or pacing, EKG evidence of myocardial ischemia, or bronchospasm) from either drug suggests that in carefully selected patients with normal or minimally impaired left ventricular function, labetalol and SNP are equivalent in rapidly and effectively controlling blood pressure.

The average dose of labetalol was 149.6 mg/patient. These high requirements are in keeping with elevated catecholamine levels following cardiopulmonary bypass and during early recovery.[2,18] This dose is considerably higher than the doses reported in studies published thus far. The cautious administration of labetalol with a slow infusion and small bolus doses given only if needed probably allowed us to use the drug safely and effectively.

Patel *et al.*[19] reported increased blood cyanide levels in seven of 292 patients undergoing CABG. The total dose of SNP in these patients varied from 157–721 mg. The SNP requirements in our patients over the 16-h period following surgery were 116 mg in the SNP group and 46 mg in the labetalol group. This difference suggests that labetalol, when used concomitantly with SNP, has the advantage of reducing the latter drug's requirements, and of avoiding potential SNP toxicity.

It is interesting to speculate that labetalol may have some advantages over sodium nitroprusside in improving the myocardial supply/demand ratio. The slower heart rate, and higher diastolic blood pressure noted in the labetalol group, with small changes in PCWP, would tend to favor improved diastolic coronary perfusion. Likewise, the slower HR would reduce myocardial oxygen demand. However, further conclusions cannot be made on the basis of our data.

In conclusion, in selected patients, labetalol compares favorably with sodium nitroprusside for the treatment of post-CABG hypertension. Its effects on myocardial oxygen balance require further study.

The authors wish to thank Drs. F. Chung and F. Leenen for reviewing the manuscript, Mr. A. Ayiomamatis for statistical analysis of the data, and Ms. C. Drane for her expert secretarial assistance.

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