A comparison of the hemodynamic effects of labetalol and sodium nitroprusside in patients undergoing carotid endarterectomy

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Introduction
Postoperative hypertension complicating carotid endarterectomy occurs in up to 64% of patients and may persist for up to 18 hours following surgery.\(^1\,^2\) Hypertension in these patients is accompanied by greater risk of myocardial infarction, cerebral vascular accident, neurologic deficit and airway compromise. Control of blood pressure for carotid endarterectomy in the perioperative period is often achieved primarily with sodium nitroprusside.\(^3\,^4\) While effective, sodium nitroprusside possesses significant side effects which potentially limit its usefulness in this setting.

Labetalol, a combined alpha- and beta-adrenergic blocker, has been found to be an effective antihypertensive agent in a variety of clinical settings.\(^5\,^6\) It has been documented to have few adverse effects when employed for the short-term management of hypertension in an acute situation.

An agent which is as effective as nitroprusside in the control of hypertension associated with carotid endarterectomy, but without its potential for serious side effects, would be an attractive alternative for clinicians. The purpose of the present study was to compare the hemodynamic effects of labetalol and sodium nitroprusside in elective carotid endarterectomy.

The hemodynamic effects of labetalol and sodium nitroprusside were compared in 19 subjects who became hypertensive at the conclusion of elective carotid endarterectomy. Following randomization and standard anesthetic protocol, treatment was administered when blood pressure exceeded 160 mmHg systolic or 90 mmHg diastolic at the conclusion of surgery. Group 1 subjects (n = 9) received 0.25 mg/kg labetalol in divided doses, followed by repeat doses of 0.50 mg/kg until blood pressure was less than 160/90 mmHg or until they had received 300 mg total dose. Group 2 subjects (n = 10) were started on a nitroprusside infusion at 0.5 μg/kg/min, titrated to achieve blood pressure less than 160/90 mmHg, or up to a rate of 6.0 μg/kg/min.

Data were collected at 15-minute intervals for 12 hours. Analysis with repeated measures analysis of covariance (p < 0.05) found no significant differences between groups in any measured parameter. A significant time effect was found for both groups.

The results suggest that labetalol is an effective alternative to nitroprusside for the management of postoperative hypertension in this patient population. For the majority of such patients, labetalol may be the drug of choice for postendarterectomy hemodynamic control.
Methods and materials

This study was approved by the Institutional Review Committee and all subjects gave their informed consent. Nineteen ASA III-IV patients presenting for elective unilateral carotid endarterectomy were studied. Excluded were those patients with:

1. Severe uncontrolled hypertension (diastolic pressure > 110 mmHg).
2. Cardiomyopathies.
3. Congestive heart failure.
4. Myocardial infarction less than six months prior to surgery.
5. Severe chronic obstructive pulmonary disease.
6. Asthma.
7. Acute neurologic deficit.

Those patients presenting for emergency carotid endarterectomy were also excluded. Patients were randomly assigned to one of the two treatment groups. Prior to entry into the study, a complete history and physical exam were performed, including chest x-ray, ECG, serum electrolyte, complete blood count with differential, urinalysis, carotid angiography, pulmonary function testing and arterial blood gas analysis.

All anesthetic procedures in the operating room were performed by the investigator. One hour prior to the beginning of surgery, all subjects received: intramuscular Versed® (midazolam) (5-10 mg) or oral Valium® (diazepam) (5-10 mg) and Reglan® (metoclopramide) (10 mg). In addition, all chronic cardiac medications were continued. In the operating room, before induction of anesthesia, an intravenous cannula was inserted and a radial arterial catheter was placed. Baseline blood pressure measurements were obtained after arterial catheter insertion and before induction of anesthesia.

All subjects were managed with the following anesthetic protocol. Prior to the induction of anesthesia, 0.5-1.0 L of either 5% dextrose in lactated Ringer's solution or lactated Ringer's solution was infused. Following preoxygenation for 5 minutes with 5 L/min of 100% O2, anesthesia was induced with fentanyl—up to 5 μg/kg intravenously (IV), sodium pentothal 1-2 mg/kg IV, and succinylcholine 1-1.5 mg/kg. Anesthesia was maintained with isoflurane 0.25-1.0%, nitrous oxide 50-60% in oxygen, and vecuronium 0.04-0.06 mg/kg IV. All subjects were placed in the semi-Fowler's position after the induction of anesthesia, with the head turned to expose the operative site. Physiologic monitoring was accomplished with V5, ECG, esophageal stethoscope and temperature probe, radial artery catheter, neural blockade monitor, inspired oxygen analyzer, pulse oximeter and spectrographic anesthetic gas analyzer. A Foley catheter was placed by the surgeon, following the induction of anesthesia, for the measurement of urine output.

At the beginning of surgical incision closure (time zero), Forane® (isoflurane) was discontinued. If patients met the entrance criteria, treatment (described later in this article) was administered and data collection was begun. Subjects were entered into the study if systolic blood pressure exceeded 160 mmHg or diastolic pressure exceeded 90 mmHg, as measured by the arterial catheter at time zero. Group 1 received 0.25 mg/kg labetalol in 10 mg increments by IV bolus, followed by 0.50 mg/kg boluses, also in 10 mg increments, administered at 1-2 minute intervals as necessary, until systolic blood pressure was less than 160 mmHg or diastolic blood pressure was less than 90 mmHg or a total dose of 300 mg was achieved. Group 2 received 0.5 μg/kg/min sodium nitroprusside by continuous infusion; the dose was titrated up to 6 μg/kg/min to achieve and maintain a systolic blood pressure of less than 160 mmHg, or a diastolic blood pressure less than 90 mmHg.

Systolic and diastolic blood pressure data were collected every 15 minutes by the placement of a 20-gauge Teflon-coated catheter in the radial artery, connected through a disposable transducer (Deseret #38-8060-1) to a Hewlett-Packard #78534B patient monitor, which features a “data management module” (Hewlett-Packard #78554A); this is a removable component which allows data transfer between monitors. The transducer cable and monitors in the operating room and intensive care unit were calibrated for each subject according to the manufacturer's instructions and rechecked every four hours during data collection.

The pressure transducer was placed at heart level during surgery and while subjects were in the surgical intensive care unit (SICU) and maintained in this position by either the investigator or by previously trained SICU nurses.

At the conclusion of surgery, subjects were awakened from anesthesia, evaluated by the surgeons for neurologic deficit and extubated. Subjects were then transferred to the SICU, where they received SICU recovery protocol during the period of the study. In the SICU, subjects were placed in a semi-Fowler's position and received oxygen at 5 L/min through a face mask. All subjects were discharged from intensive care on the first postoperative day and all recovered uneventfully.

Statistical analysis was performed with two tailed t-test and chi-square test for demographic data. Repeated measures analysis of covariance (ANCOVA) was used to analyze mean differences in systolic, diastolic, mean blood pressure and heart
rate following treatment; systolic, diastolic, mean
blood pressure and heart rate at time zero served as
covariates. In all cases, significance was set as
p<0.05.

Results
There were no significant differences between
groups in any demographic parameter (Tables 1
and 2). The mean dose of labetalol required to
reach the target blood pressure (less than 160 mmHg
systolic or 90 mmHg diastolic) was 64.0 ± 28.5
mg/kg (mean ± standard error), with a range of
10-300 mg. No additional labetalol was required for
any patient in Group 1 for the duration of the study
after the initial loading dose had been achieved.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.3 ± 2.6</td>
<td>62.9 ± 2.1</td>
</tr>
<tr>
<td>Weight (pounds)</td>
<td>170.4 ± 10.0</td>
<td>169.7 ± 7.8</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>5/5</td>
<td>7/2</td>
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<tr>
<td>Preoperative measurements (mmHg)</td>
<td></td>
<td></td>
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<tr>
<td>Systolic pressure</td>
<td>160.4 ± 8.2</td>
<td>170.6 ± 9.0</td>
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<tr>
<td>Diastolic pressure</td>
<td>70.6 ± 4.3</td>
<td>79.4 ± 3.5</td>
</tr>
<tr>
<td>Mean pressure</td>
<td>100.6 ± 5.3</td>
<td>110.4 ± 5.8</td>
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</table>

SNP—sodium nitroprusside
No significant differences were found between groups
in any demographic parameter. All measurements except
sex are mean ± standard error, p < 0.05.

<table>
<thead>
<tr>
<th>Preoperative use of antihypertensive medications (yes/no)</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>0/10</td>
<td>3/6</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>4/6</td>
<td>6/3</td>
</tr>
<tr>
<td>Other antihypertensives</td>
<td>8/2</td>
<td>8/1</td>
</tr>
<tr>
<td>Preoperative ECG evidence of bradycardia</td>
<td>0/10</td>
<td>5/4*</td>
</tr>
</tbody>
</table>

SNP—sodium nitroprusside
*Four of the 5 patients who had
evidence of bradycardia were on beta blockers.
No significant differences were found between groups
in any demographic parameter (p < 0.05).

Discussion
The present study has demonstrated the clinical
efficacy of labetalol in carotid endarterectomy.
Labetalol appears to offer a hemodynamic profile
comparable to that of nitroprusside when commonly
employed clinical dosages are given and, thus, is an
attractive alternative to nitroprusside in this
population.

Hypertension accompanying carotid endarterectomy occurs in up to 64% of patients. When com-
pared to patients who remain normotensive after
carotid endarterectomy, postoperative hyperten-
sives have greater morbidity and mortality, greater
risk of myocardial infarction, neurologic deficit and
airway compromise. The risk period is gener-
ally up to 18-20 hours postoperatively, with the first
Four postoperative hours being crucial. Rigid perioperative control of blood pressure is advocated to avoid or minimize complications.

The standard agent for blood pressure control in carotid endarterectomy has been sodium nitroprusside. The very short duration of action allows for rapid adjustment of blood pressure in the carefully monitored patient. While effective, nitroprusside has the potential for serious side effects. Hypotension, secondary to rapid administration or inadvertent bolusing, may exacerbate myocardial ischemia and intrapulmonary shunting and may
compromise cerebral perfusion. The hyperdynamic response to nitroprusside, characterized by reflex tachycardia and increased cardiac output, may compromise the balance between myocardial oxygen supply and demand in the susceptible patient. Beta blockade or therapy with other vasodilators is often required to attenuate this response.

Nitroprusside tachyphylaxis is a widely reported phenomenon, manifested by metabolic acidosis and higher doses being required for maintenance of desired blood pressure. Tachyphylaxis has been reported to occur at high dose rates or after prolonged administration. However, recent evidence suggests that tachyphylaxis may occur at dose rates as low as 4 μg/kg/min and after as little as six hours exposure. In addition, the appearance of tachyphylaxis may be unpredictable.

The hemodynamic effects of labetalol, a combined alpha- and beta-adrenergic antagonist, have been investigated in many settings. It has been employed in coronary artery bypass surgery, hypertension complicating myocardial infarction, hypertension complicating angina pectoris, hypertensive emergencies and hypertensive emergencies complicating congestive heart failure. In all studies cited, normal blood pressures were achieved without evidence of side effects or change in heart rate. Labetalol is thought to possess significant myocardial protective effects by improving coronary hemodynamics, decreasing myocardial oxygen consumption and by decreasing systemic vascular resistance. It has also been suggested that labetalol is significantly less expensive to administer than nitroprusside.

A recent study by Goldberg et al. examined the effect of labetalol on postoperative hypertension complicating carotid endarterectomy. Seventeen patients who met entrance criteria (systolic pressure ≥200 mmHg or ≥20% over baseline; diastolic pressure ≥100 mmHg) were given a mean dose of 41.2 ± 32.0 mg labetalol by bolus injection. Statistically significant decreases in heart rate and systolic, diastolic and mean pressures were seen following treatment. It was concluded that labetalol was useful for treating hypertension in the population of carotid endarterectomy patients. Goldberg et al. also measured serum catecholamines and found that norepinephrine levels were significantly higher in those patients who became hypertensive after carotid endarterectomy, compared with normotensive postcarotid endarterectomy patients. While treatment with labetalol did not lower plasma norepinephrine levels, consistent with the adrenergic receptor site of action for labetalol, the observed significant blood pressure reductions suggest that labetalol is specific for treating hypertension in this setting.

The present study demonstrated that labetalol and nitroprusside produced comparable hemodynamic profiles in this population, but they appear to have different clinical effects. As seen in Figures 1-3, systolic, diastolic and mean pressure fell rapidly in the first 30 minutes following initiation of treatment with nitroprusside. In contrast, blood pressure was maintained in the 30 minutes following treatment (at pretreatment levels after bolus injection of labetalol). Emergence from anesthesia occurred between 15-30 minutes posttreatment for all patients.

The divergent response curves reflect the different potencies of the drugs and offer insight into their administration. Nitroprusside was more effective in lowering pressure during this stressful event, while labetalol prevented further increases in pressure during emergence. Following emergence, the hemodynamic profiles were similar.

The results of this study offer support for the use of labetalol in this population. Nitroprusside is effective, but must be continually titrated and monitored. Labetalol, on the other hand, appears to offer comparable clinical effectiveness, but without the dangers inherent in extreme potency or with the use of pumps for administration. The anesthetist generally administers these agents during carotid endarterectomy at a point when attention must be given to several equally important facets of emergence. Labetalol may be given by bolus injection and has a lower potential for side effects. Such side effects tend to be mild when they occur. Literature review indicates that the use of labetalol for management of acute hypertensive episodes, as opposed to chronic therapy with the drug, is rarely associated with significant side effects such as excessive bradycardia, decreased cardiac output, bronchospasm, nausea and postural hypotension. As noted above, none of the studies cited for this article had significant side effects associated with the use of labetalol in an acute clinical setting.

A significant relative diastolic hypotension with nitroprusside was observed at 30 minutes posttreatment. Since this was during emergence from anesthesia, it demonstrates the ability of nitroprusside to attenuate the hypertensive response to emergence. This may also reflect some difficulty in titrating nitroprusside while other events of emergence were occurring and with diastolic pressure falling as a result of brief relative overdose. Labetalol, in contrast, prevented an increase in pressure at this point. When the data from two subjects in the labetalol group (both with poorly controlled preoperative hypertension) were subtracted from...
the analysis, the curves for labetalol and nitroprusside were similar and differences were not significant.

A significant contribution to mean scores was seen for pretreatment heart rate (covariate). Sixty-six percent of the nitroprusside group (6 of 9) were on preoperative beta blockers, as opposed to 40% of the labetalol group (4 of 10). In addition, 5 of 9 nitroprusside patients had preoperative ECG evidence of bradycardia, though 4 of those 5 were on beta blockers as well. None of the labetalol group demonstrated sinus bradycardia on the preoperative ECG. Once this effect was statistically controlled, no difference was seen between groups for heart rate. Since all observed heart rates were within the normal range, the significant group/time interaction at 9 hours posttreatment most likely represents group differences in intrinsic heart rate and does not reflect differences in treatment (Figure 4).

The significant change over time for the entire sample observed in all parameters probably reflected a return to normal blood pressure and heart rate levels for all subjects. As has been noted above, the duration of action for labetalol is 3-5 hours. In the present study, the mean duration of nitroprusside infusion was 4.4 ± 1.5 hours. It is felt that labetalol and nitroprusside both protected the subjects in the early postoperative period from the development or sustenance of clinically significant hypertension. The gradual drop in pressure and heart rate over time represented a return of normal homeostatic mechanisms. This return of baroreceptor function coincided with, in the case of labetalol, the termination of pharmacologic effects as the drug effect wore off. The same phenomenon was seen with nitroprusside but with one clinically significant difference. As pressure returned to normal in Group 2, the infusion had to be tapered off and then discontinued; this is the vigilance required with nitroprusside. The patient has the potential to be subjected to, at a minimum, an unnecessary infusion of a possibly toxic agent or to an incident of disastrous hypotension. The observed time effect offers further support for the use of labetalol in this population. A single administration of labetalol may offer a period of protective effects which coincides with the return of normal blood pressure homeostatic mechanisms. Further study of this phenomenon is indicated.

Because of the observed clinical efficacy of labetalol, comparable to nitroprusside, the greater ease of administration, lower incidence of side effects, wider margin of safety and potential economic savings, it is felt that labetalol is an attractive alternative to nitroprusside for the management of postoperative hypertension in this patient population. For those in whom beta blockade is not contra-indicated, labetalol may be the drug of choice for postcarotid endarterectomy hemodynamic control.

REFERENCES


(27) Morel DR, Forster A, Suter PM. 1982. IV labetalol in the treatment


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