Low-Dose (1 μg/kg) Clonidine Premedication and Hypotension After Carotid Artery Surgery

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Abstract
We investigated the role of low-dose clonidine intravenous (IV) premedication in arterial pressure variation during and after carotid endarterectomy (CEA). A total of 84 patients, American Society of Anesthesiologists (ASA) II-III, scheduled for elective CEA under general anesthesia participated in this study. The patients were divided into 2 groups: group P (n = 42) and group C (n = 42) and received N/S 0.9% (placebo) or clonidine 1 μg/kg IV, respectively, 15 minutes before induction of anesthesia. Recovery times, number of patients needed to be treated for circulatory events (hypertension, hypotension, and bradycardia), number of circulatory events per patient, and consumption of vasoactive drugs (nitroglycerine, phenylprine, and atropine) intraoperatively and the first 6 hours postoperatively were recorded. Significantly less hypertensive episodes were observed intraoperatively, but more hypotensive episodes were observed postoperatively in patients receiving clonidine. Intravenous premedication with low-dose clonidine (1 μg/kg) seems to be effective in preventing hypertensive episodes during CEA under general anesthesia but seems to increase the incidence of hypotension postoperatively.

Keywords
clonidine, carotid endarterectomy, blood pressure variability

Introduction
Disease of the carotid artery has the unique characteristic of involving the baroreceptors of the carotid sinus, one of the principal components of the physiological control mechanism of arterial pressure, in the disease process itself. The above makes arterial pressure control often difficult.1,2 Up to 66% of patients usually develop transient hypertension in the first few hours after CEA (40% of them need treatment), while 75% of patients have significant episodes of hypotension (>30 mm Hg decrease in systolic blood pressure [SAP]) within the first 24 hours of carotid revascularization.2

Most studies emphasize on the hypertension control during and after CEA in order to prevent myocardial ischemia and cerebral injury.3,4 However, precipitous decreases in arterial pressure should also be avoided, since they can be associated with augmentation of the ischemic effect of microembolic events and watershed cerebral ischemia.5,6 Antihypertensive drugs should therefore be given in a controlled manner and titrated against effect, in order to avoid excessive hypotension. Patients with carotid artery disease tend to be elderly and have a high incidence of coexisting diseases such as diabetes mellitus and hypertension, which render them more sensitive to the hypotensive effects of antihypertensive drugs.1,7 An agent that can prevent hypertensive episodes without leading to hypotension during and after CEA is therefore needed.

Clonidine, an α-2 receptor agonist, has been used before or during various types of surgery as an agent with an ability to decrease arterial pressure, myocardial ischemia, and plasma catecholamine concentrations.8 There are only 2 studies, to our knowledge, examining the effect of clonidine on hemodynamic stability during and after CEA under general anesthesia: oral clonidine premedication (4 μg/kg) did not prevent hemodynamic variability during CEA, while 3 μg/kg administered IV 30 minutes before the end of the operation decreased

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hypertensive episodes after CEA but predisposed to postoperative hypotension. 9,10

Our study aimed at investigating whether a different dose of clonidine, lower than those previously used, would be effective in both suppressing hypertensive episodes and minimizing the risk of hypotension during operation and the first hours after CEA under general anesthesia. We also investigated the impact of this dose of clonidine on myocardial ischemia.

Materials and Methods

The protocol was approved by the ethics committee of Attikon Hospital and written informed consent was obtained from patients. Our primary goal was to detect the effect of clonidine on blood pressure after CEA. We determined that we needed 40 patients per group in order to detect 40% difference in vasopressor (phenylephrine) consumption between the two groups and have a level of 0.05 and a power of 90%. We enrolled 84 patients, American Society of Anesthesiologists (ASA) status II or III, scheduled for elective CEA under general anesthesia because of a narrowing of the carotid artery lumen of ≥80% in asymptomatic or ≥70% in symptomatic patients. Exclusion criteria were a history of severe cardiac disease or abnormality in cardiac conduction, severe respiratory or renal insufficiency, and treatment with clonidine, guanabenz, rilmelidine, methyl-dopa, or reserpine. The study was a prospective, randomized, double-blind investigation using sealed envelopes for randomization. The patients were divided into 2 groups: (1) The patients were divided into 2 groups: (1) group P (n = 42) and (2) group C (n = 42) and received N/S 0.9% (placebo) or clonidine 1 mg/kg, respectively, intravenously during a period of 15 minutes, 15 minutes before induction of anesthesia. Drugs were prepared by a nurse who did not participate in the patients’ treatment. All procedures were performed by the same anesthetic and surgical team.

With the exception of angiotensin-converting enzyme inhibitors (stopped 1 day before the operation), all antihypertensive drugs were continued until the morning of the operation. On the morning of the surgery, all patients were given 50 mg of hydroxyzine and 150 mg of ranitidine orally, 90 minutes before induction. In the operating room, 2 IV catheters were inserted and the radial artery was cannulated. Besides the standard monitoring (a 5-lead electrocardiograph [ECG], pulse oximetry, noninvasive blood pressure measurement), Bispectral Index ([BIS] A-2000, Aspect, Newton, New Jersey) and INVOS Cerebral Oximeter (Somanetics, Model 5100B, Troy, Michigan) monitors were also applied. All patients received midazolam 0.02 mg/kg upon arrival in the operating room and 5 mL/kg of a Ringer lactated solution IV before induction.

In both groups, induction of anesthesia was performed with fentanyl 2 μg/kg and etomidate 0.2 to 0.3 mg/kg, until the BIS reached a value below 40. Tracheal intubation was facilitated by cis-atracurium 0.2 mg/kg. Anesthesia was maintained with desflurane in 40% oxygen in air in order to keep the BIS values between 40 and 50. Patients’ lungs were ventilated to maintain normocapnia (end-expiratory carbon dioxide between 35 and 45 mm Hg). Five minutes before skin incision, another 1 μg/kg of fentanyl was injected. Paracetamol 15 mg/kg was given intramuscularly 30 minutes before the end of operation to provide for postoperative analgesia. Monitoring included continuous ST segment analysis of leads II and V, inspiratory and end-tidal desflurane and carbon dioxide concentration, invasive blood pressure, BIS, and INVOS Cerebral Oximeter. ST-segment depression was defined as horizontal or downslopping ST segment depression of 1 mm or more extending at least 60 ms beyond the J point and lasting >60 seconds.

A shunt was used selectively, when the stump pressure (pressure measured in the internal carotid artery once the common and external carotid arteries were clamped) was found to be <40 mm Hg. A phenylephrine infusion was initiated, if needed, to increase the mean arterial pressure (MAP) by 25% above baseline (defined as the average of 2 preoperative measurements on the day before surgery), while the carotid artery was clamped. Hypertension was defined as a 30% increase of SAP above baseline lasting more than 1 minute. It was treated with nitroglycerine IV (0.25-2.5 μg/kg per min). Hypotension was defined as a 30% decrease in SAP below baseline more than 1 minute and was treated with phentolamine 40 to 80 μg IV, which was repeated until the blood pressure restored to required values. Bradycardia (heart rate [HR] <40) was treated with atropine 0.5 mg.

After emergence from anesthesia, patients were transferred to postanesthesia care unit (PACU) and kept under observation for the first 6 hours postoperatively. Invasive blood pressure, a 5-lead ECG and continuous ST segment analysis of leads II and V and pulse oximetry were monitored in the PACU. The patients were kept normotensive (accepted range: SAP > 100 mm Hg and SAP < 170 mm Hg) with the aid of fluid infusion or treatment with vasoactive drugs (phenylephrine or nitroglycerine).

The following parameters were recorded: demographic data, duration of anesthesia, surgery and clamping, total fluid consumption, times from switching off the vaporizer of desflurane to extubation, movement on command of a leg or arm on the side opposite to that of the surgery and verbal communication (appropriate response to the questions, what is your name? and Where are you?), number of patients needed to be treated for hemodynamic events (hypertensive and hypotensive), number of hemodynamic episodes per patient, and consumption of vasoactive drugs (nitroglycerin, phenylephrine, and atropine). We also recorded any ST depression (≥1 mm) or elevation (≥2 mm) lasting more than 1 minute during the total period of our observation, and we measured plasma levels of troponin I, creatine kinase, and its MB isoenzyme preoperatively 12 and 24 hours postoperatively. In the PACU, Ramsay score for sedation (0-4) was recorded every hour and the severity of nausea and pain was judged by a verbal analogue scale 0 of 10. Nausea score >4 or vomiting was treated with ondansetron 4 mg IV, and pain score >4 was treated with parecoxibe 40 mg IV. Any cardiac or neurological complication during patients’ hospitalization was also recorded.

Statistical analyses were performed with SPSS 13.0 for Windows (SPSS Inc, Chicago, Illinois). Results are expressed as mean ± standard deviation (SD), mean (95% confidence interval

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[CI of mean], or number of patients (%) as appropriate. Normally distributed data were analyzed using Student t test or analysis of variance (ANOVA) for repeated measurements, whereas for the analysis of categorical and skewed data $\chi^2$ test, Mann-Whitney $U$ test, or Kruskal-Wallis tests were used as appropriate. A $P$ value of <.05 was considered statistically significant.

Results
The 2 groups were comparable for demographic, preoperative, and intraoperative characteristics (Tables 1 and 2). A shunt was used in 2 patients in group P and 1 patient in group C. There was also no difference in intraoperative end-expiratory desflurane concentration (Table 2).

Significantly less patients receiving clonidine presented with at least 1 hypertensive episode and needed to be treated with nitroglycerine intraoperatively, while the total number of hypertensive episodes was also significantly reduced in this group (Table 3). On the contrary, significantly more hypotensive episodes were observed postoperatively in patients with clonidine and the number of clonidine-treated patients who developed at least 1 hypotensive episode postoperatively and needed to be treated with phenylephrine was also significantly more (Table 3). Total consumption of phenylephrine was significantly higher in the clonidine group, both intraoperatively and postoperatively (Table 3). We should mention that phenylephrine was also used intraoperatively in order to increase MAP by 25% above baseline while the carotid artery was clamped. This might explain the lack of difference in the number of patients needed to be treated with phenylephrine intraoperatively. However, the fact that more phenylephrine was used intraoperatively may be attributed to the tendency for low pressure in clonidine-treated patients. More patients receiving clonidine needed to be treated with atropine (Table 3).

Emergence times were comparable between patients of the 2 groups, except of the time for movement of an extremity (Table 3).
receiving clonidine (Table 4). Occurrence of pain, nausea, or vomiting postoperatively was comparable in the 2 groups. There was also no difference in sedation scores between the 2 groups.

No significant ST segment changes were observed preoperatively, and creatine kinase MB (CK-MB) and troponin measurements were within normal values in both groups (Table 5). However, CK was found significantly lower in the clonidine group (Table 5). In spite of normal perioperative ECG, 1 patient in the placebo group developed perioperative angina pectoris, which resolved without further deterioration. No patient presented with a neurologic event.

**Discussion**

A major concern of the anesthetic management during CEA is the maintenance of normotension, since arterial baroreflex activity may be stimulated or depressed, leading to the development of hypertension or hypotension.1 There is indirect evidence that prompt control of arterial pressure in patients who are hypertensive after CEA improve the outcome by reducing neurological complications, wound complications, or both, and most practitioners would consider rapid treatment of postoperative hypertension to be important.7 Hypotension during or after CEA, on the other hand, should be avoided. It leads to brain hypoperfusion which augments the ischemic effects of gaseous or particulate microemboli that occur mainly during the initial dissection phase of CEA. Emboli and hypoperfusion are mechanisms that may be involved in the decline of cognitive function after CEA.11

It is known that the arterial baroreflex plays an important role in the prevention of excessive blood pressure swings, as it acts as an effective buffer of short-term blood pressure fluctuations.12 A surgical technique, therefore, that maintains the carotid sinus nerves and avoids local anesthetic infiltration and the administration of an agent able to preserve baroreflex activity are desirable in order to avoid excessive blood fluctuations during CEA. The first 2 conditions were fulfilled by surgeons in both groups of our study and the agent chosen was clonidine. Because of its pharmacologic characteristics (long-lasting effects on blood pressure) and positive effects (reduction in myocardial oxygen consumption, lower incidence of shivering, cerebroprotective effects, attenuation of the pressor, and tachycardic surges in baroreflex failure), clonidine would seem to be an ideal antihypertensive drug in carotid artery surgery.13,14 Other agents such as direct-acting vasodilators (eg, sodium nitroprusside, glyceryl trinitrate, nicardipine, and hydralazine), although widely used, have theoretical disadvantages after CEA as they cause cerebral vasodilatation. Nifedipine capsules also cause cerebral vasodilatation and precipitous decreases in arterial pressure, which have been associated with serious adverse events. Unfortunately, clonidine may also have dose-related hypotensive effects.7

A major concern therefore during the design of our study was the choice of the appropriate dose of clonidine that would be effective in decreasing hypertensive episodes during CEA without causing hypotension. According to Marinangeli et al,15 the optimal dose of clonidine is 3 μg/kg. However, this dose was administered IV 30 minutes by previous investigators before the end of CEA under general anesthesia and caused hypotension.9 We decided therefore to administer 1 μg/kg clonidine IV, which is the dose that did not cause significant reduction in MAP and HR in healthy volunteers, compared to 2 and 4 μg/kg.14 We found that our dose of clonidine was effective in preventing hypotension during CEA but did not prevent the development of hypotension or hypertension postoperatively. Our results agree with Wallenborn et al, as far as the cause of hypotension postoperatively is concerned, but they also proved in the control of hypertension.9 The different dose and timing of administration may explain our differences. On the other hand, Pluskwa et al did find any beneficial effect of 4 μg/kg clonidine oral premedication in intraoperative cardiovascular stability.10 Our different results may be attributed to the different routes of clonidine administration (IV vs oral administration).

Postoperative hypotension in patients undergoing CEA under general anesthesia may be caused by residual effects of anesthetic drugs, overzealous pharmacological treatment of hypertension, low-cardiac output states (vasovagal episodes, cardiac failure, and myocardial infarction), or hypovolemia (bleeding into the surgical drain).7

The anesthetic agent used in our study was desflurane, a short-acting agent that has little residual effects and has also showed advantages in the recovery times and the possibility of a quick postoperative neurologic examination when used during CEA.16 Cardiovascular causes and hypovolemia are excluded for the patients of our study, except for the prevalence of bradycardia in the patients treated with clonidine. Therefore, postoperative hypotension can be attributed to the effects of our antihypertensive agent.

**Table 5. Cardiac Enzymes Measurements**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Baseline (Preoperatively)</th>
<th>12 hours Postoperatively</th>
<th>24 hours Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>P</td>
</tr>
<tr>
<td>Trop I</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>.264</td>
</tr>
<tr>
<td>CK (U/mL)</td>
<td>68.2 ± 35.3</td>
<td>59 ± 26.9</td>
<td>123.7 ± 69.3</td>
</tr>
<tr>
<td>CK-MB (U/mL)</td>
<td>13.3 ± 4.5</td>
<td>11.8 ± 4.3</td>
<td>13.2 ± 3.5</td>
</tr>
</tbody>
</table>

Abbreviations: Trop I, troponin I; group A, patients receiving placebo; group B, patients receiving clonidine; CK, creatine kinase; SD, standard deviation.

*Data are expressed as mean ± SD.*
In order to avoid anesthetic overdose and a higher incidence of the need for vasopressors during intraoperative unstimulated periods in the clonidine group, we used BIS to monitor anesthetic depth.\textsuperscript{13,14} Bispectral Index monitor use led to the absence of difference in end-expiratory desflurane concentration between our groups.

There is still controversy over the prolongation of recovery times by clonidine.\textsuperscript{15} Our study showed a statistical significant prolongation of the time for movement on command (approximately 2.5 minutes) with the administration of clonidine. Awakening and neurologic examination immediately after the operation was also delayed by clonidine in the previous studies.\textsuperscript{9,10} However, we think that avoidance of hypertensive crisis has priority over moderate prolongation of awakening times.

The reduction in ischemic cardiac events by clonidine has already been confirmed by meta-analyses.\textsuperscript{17} The expected incidence\textsuperscript{18} for myocardial infarctions in the population undergoing CEA is approximately 2%. However, no perioperative myocardial infarction was observed during this clinical study. Furthermore, we observed a reduction in CK in patients receiving clonidine. Although our sample size is too small to establish a cardioprotective effect of clonidine, the above indications are promising.

In conclusion, IV premedication with low-dose clonidine (1 \( \mu \)g/kg) seems to be effective in preventing hypertensive episodes during CEA under general anesthesia, but increases the incidence of hypotension postoperatively.

**Declaration of Conflicting Interests**

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**References**


