A randomized trial of two doses of nicardipine in aneurysmal subarachnoid hemorrhage

A report of the Cooperative Aneurysm Study

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High-dose intravenous nicardipine has been shown to reduce the incidence of angiographic and symptomatic vasospasm in patients with aneurysmal subarachnoid hemorrhage (SAH), but treatment may be complicated by side effects, including hypotension or pulmonary edema/azotemia. From August, 1989, to January, 1991, 365 patients at 21 neurosurgical centers were entered into a randomized double-blind trial comparing high-dose (0.15 mg/kg/hr) nicardipine with a 50% lower dose (0.075 mg/kg/hr) administered by continuous intravenous infusion for up to 14 days following SAH. Patients in all neurological grades were eligible for the study.

During the study period, 184 patients were randomly assigned to receive high-dose nicardipine and 181 to receive the low dose. There were no significant differences in patient age, admission neurological condition, or amount and distribution of blood clot on initial computerized tomography scan. Patients in the high-dose group received a significantly smaller proportion of the planned dose than those in the low-dose group (80% ± 0.2% vs. 86% ± 0.2%, p < 0.05), largely because of premature treatment termination after adverse medical events. The incidence of symptomatic vasospasm was 31% in both groups, and the overall 3-month outcomes were nearly identical. These data suggest that, from a clinical standpoint, the results of high-dose and low-dose nicardipine treatment are virtually equivalent, but administration of low-dose nicardipine is attended by fewer side effects.

Key Words: nicardipine · subarachnoid hemorrhage · cerebral aneurysm · calcium antagonist · vasospasm

Calcium antagonist drugs, such as the dihydropyridine antagonists nimodipine and nicardipine, have been increasingly employed as adjuncts in the management of patients with aneurysmal subarachnoid hemorrhage (SAH). Recently it was shown in a large multicenter randomized double-blind placebo-controlled trial that treatment with large doses of intravenous nicardipine administered as a continuous infusion for 14 days following SAH was associated with a reduction in symptomatic, as well as angiographic, vasospasm. However, adverse side effects, including hypotension, pulmonary edema, and renal dysfunction, led to premature discontinuation of nicardipine in 14% of patients. Premature discontinuation of nicardipine treatment was not infrequently followed by the onset of ischemic neurological deficits in this unprotected population.

Since the dose of nicardipine administered in the placebo-controlled trial was nearly 10 times higher in biological equivalents than the currently recommended dose of nicardipine for SAH patients (Syntex Research, unpublished data), the present study was undertaken to examine whether a 50% lower dose of nicardipine might be equally (or perhaps more) effective in preventing ischemic deficits from vasospasm and, at the same time, safer in terms of a reduced number and severity of side effects. The results of this randomized double-blind trial of high-dose versus 50% dose of nicardipine in patients with recent aneurysmal SAH are the subject of this report.

Clinical Material and Methods

Patient Selection

Patients for this study were selected from all patients with SAH admitted to 23 hospitals in 21 centers in the...
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United States and Canada.* The study protocol and informed consent form were approved for use by each institution's Institutional Review Board. Criteria for entry were identical to those in the placebo-controlled trial published previously. Briefly, a patient was eligible for the study if: 1) the patient was aged 18 years or older; 2) SAH was confirmed by computerized tomography (CT) or lumbar puncture (all neurological grades were eligible); 3) angiography demonstrated a saccular aneurysm; and 4) the patient could begin therapy at a participating hospital between Days 0 and 7 (Day 0 being the calendar day of the hemorrhage) following the most recent hemorrhage.

A patient was excluded from the trial if: 1) the aneurysm was fusiform, traumatic, or mycotic; 2) severe complicating medical illnesses were present; 3) the patient was receiving a calcium antagonist drug at the time of the hemorrhage; 4) the patient had suffered another neurological or psychiatric illness that might confound the neurological evaluation; 5) the patient had a history of allergy to or intolerance of calcium antagonist drugs; 6) the patient was known or suspected to be pregnant; or 7) legal informed consent could not be obtained.

**Randomization**

After initial screening was performed and informed consent obtained, eligible patients were randomly assigned in equal ratio to receive either standard high-dose (0.15 mg/kg/hr) or low-dose (0.075 mg/kg/hr) nicardipine by continuous intravenous infusion for up to 14 days following SAH, at which time the infusion was to be discontinued. The nicardipine preparations were diluted to equal volumes to preserve study blinding. Blocked random assignment to the two treatment groups was accomplished within each center. The randomization sequence was generated by Syntex Research and was kept blinded from the staff of the Central Registry of the Cooperative Aneurysm Study as well as the participating investigators until the study had been completed and the data audited and finalized.

**Study Drug Regimen**

If clinically feasible, all patients received 500 cc of colloid solution just prior to the beginning of study drug infusion in order to ameliorate any hypotensive side effects attending nicardipine administration. Following colloid infusion, the study drug infusion was begun at one-half the planned infusion rate and maintained for 8 hours. If no signs of intolerance developed, the infusion rate was increased to 75% of the planned rate for another 8 hours, and then finally to the full dose. If intolerance developed, as evidenced by hypotension or other adverse effects, the dosage rate was titrated back by 50% and then either increased again or discontinued if adverse effects persisted. Blood urea nitrogen was monitored at least every other day; if it exceeded 30 mg/dl, the dose was halved or discontinued.

Thus, all patients were to receive the full planned dose or the maximally tolerated fraction of the planned dose.

Use of any other calcium antagonist during the treatment period was prohibited. Conventional therapy for symptomatic vasospasm, such as intentional hypervolemia (prophylactically or therapeutically), induced hypertension, and/or mannitol administration, was allowed at the discretion of the treating investigator. Experimental therapies for vasospasm, such as angioplasty or intraarterial thrombolytic therapy, were prohibited. Decisions regarding the timing of aneurysm surgery and the use of antifibrinolytic drugs, steroids, or other adjunctive therapies were left to the participating investigators.

**Endpoints**

Endpoints examined for the study were complication rates, rates of premature discontinuation of study drug, incidence of ischemic deficits due to vasospasm (symptomatic vasospasm), incidence of death and disability due to vasospasm, incidence and volume of infarction on a CT scan obtained at 3 months, overall outcome at 3 months as assessed according to the Glasgow Outcome Scale (GOS) by a blinded evaluator, and the results of a graded neurological examination (National Institutes of Health (NIH) Stroke Scale and Folstein Mini-Mental State). Symptomatic vasospasm was diagnosed using clinical criteria.*

**Patient Monitoring**

The incidence of neurological worsening during the treatment period was also monitored. Neurological worsening was defined as a decline of two or more points in the daily modified (all four limbs scored for motor score) Glasgow Coma Scale score or an increase of two or more points in the motor score on the NIH Stroke Scale. When neurological worsening was recognized, the investigators were required to designate a primary cause and all contributing causes, as well as the treatment initiated for the neurological worsening.

**Angiographic Studies**

Copies of cerebral angiograms obtained for clinical indications between Days 7 and 11 following SAH were sent to the Central Registry for blinded measurement of the incidence and severity of angiographic vasospasm. Angiographic vasospasm, if present, was graded as mild, moderate, or severe. Additionally, if transcranial Doppler ultrasound studies were available, mean blood flow velocity in each middle cerebral artery (MCA) was measured and recorded at baseline, between Days 7 and 11, on Day 14, at the time of neurological worsening, and at additional times if clinically indicated.

**Data Analysis**

A t-test was used to analyze continuous data. Contingency table data were analyzed with the chi-squared test or in the case of sparse information, with Fisher's exact test. Ordinal scales such as the NIH Stroke Scale and Folstein Mini-Mental State were compared with

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* Participating centers and personnel are listed in the Appendix.
the Kruskal-Wallis test. The Kaplan-Meier method was used to generate mortality curves, and comparisons were made with the log rank test. All tests used a significance level of 0.05.

Results

From September, 1989, to January, 1991, 365 patients were entered into the trial. The trial was terminated before the planned 600 patients were accrued because of problems discovered with the shelf life of the nicardipine supplies. The lowest detected potency in the study drug supply was 86% of the labeled concentration. The majority (73%) of the patients in the trial received full potency (> 90%) of the drug.

During the entry period, 397 patients with SAH admitted to the participating centers were excluded from the study. Reasons for exclusion were: lack of angiographic demonstration of an aneurysm (27%); use of another calcium antagonist at the time of SAH (17%); presence of other severe complicating illnesses (15%); study accrual temporarily suspended (12%); inability to begin therapy within 7 days of SAH (6%); presence of a nonsaccular aneurysm (4%) and inability to obtain informed consent (4%). Other exclusion criteria were present for 10% of these patients, with each comprising less than 3%. Patients may have had more than one exclusion criterion.

Of the 365 study subjects, 184 were randomly assigned to receive standard dose nicardipine (high-dose group) and 181 were assigned to receive 50% of the standard dose (low-dose group). Table 1 shows the admission characteristics and prognostic factors for vasospasm and outcome in the patients in each group. There were proportionally more women in the low-dose group (74% vs. 61%, p < 0.01), and the mean height and weight of the patients in this group were less than in the high-dose group. There were no statistically significant differences in mean patient age, admission neurological condition, admission systolic or diastolic blood pressure, or the amount and distribution of blood clot present on the admission CT scan.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Low-Dose Group†</th>
<th>High-Dose Group†</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>181</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>181</td>
<td>184</td>
<td>0.09</td>
</tr>
<tr>
<td>Alert or drowsy</td>
<td>179</td>
<td>185</td>
<td>0.67</td>
</tr>
<tr>
<td>Oriented</td>
<td>175</td>
<td>180</td>
<td>0.16</td>
</tr>
<tr>
<td>WFNS Grade‡</td>
<td>180</td>
<td>184</td>
<td>0.84</td>
</tr>
<tr>
<td>I</td>
<td>85</td>
<td>47.2</td>
<td>0.45</td>
</tr>
<tr>
<td>II</td>
<td>33</td>
<td>18.3</td>
<td>0.22</td>
</tr>
<tr>
<td>III</td>
<td>18</td>
<td>10.0</td>
<td>0.54</td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
<td>10.0</td>
<td>0.54</td>
</tr>
<tr>
<td>V</td>
<td>26</td>
<td>14.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Admitted post-SAHerit, Day 0-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>181</td>
<td>146 ± 24.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic</td>
<td>180</td>
<td>83.4 ± 14.4</td>
<td>0.92</td>
</tr>
<tr>
<td>Subarachnoid clot on CT</td>
<td>176</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>15</td>
<td>8.5</td>
<td>0.27</td>
</tr>
<tr>
<td>Present</td>
<td>161</td>
<td>91.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Subarachnoid clot grade</td>
<td>155</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Diffuse thin deposition</td>
<td>45</td>
<td>29.0</td>
<td>0.83</td>
</tr>
<tr>
<td>Diffuse thick deposition</td>
<td>60</td>
<td>38.7</td>
<td>0.40</td>
</tr>
<tr>
<td>Localized thin layer (&lt; 1 mm)</td>
<td>21</td>
<td>13.6</td>
<td>0.10</td>
</tr>
<tr>
<td>Localized thick layer (&gt; 1 mm)</td>
<td>29</td>
<td>18.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Intraventricular clot on CT</td>
<td>176</td>
<td>55</td>
<td>31.3</td>
</tr>
<tr>
<td>Intraparenchymal clot on CT</td>
<td>176</td>
<td>8</td>
<td>4.6</td>
</tr>
</tbody>
</table>

* SAH = subarachnoid hemorrhage; CT = computerized tomography. Mean values are expressed ± standard deviation.
† Total = number with available data; No. and % = number and percent with indicated prognostic factor.
‡ World Federation of Neurological Surgeons (WFNS) SAH scale.
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**TABLE 3**
Concomitant management practices in each study group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Low-Dose Group</th>
<th>High-Dose Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases*</td>
<td>181</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>anticonvulsant drugs</td>
<td>158</td>
<td>159</td>
<td>0.87</td>
</tr>
<tr>
<td>steroids</td>
<td>137</td>
<td>134</td>
<td>0.71</td>
</tr>
<tr>
<td>antifibrinolytic drugs</td>
<td>20</td>
<td>10</td>
<td>0.06</td>
</tr>
<tr>
<td>antihypertensive drugs</td>
<td>54</td>
<td>61</td>
<td>0.43</td>
</tr>
<tr>
<td>hypertensive/hypervolemic/hemodialysis therapy</td>
<td>119</td>
<td>123</td>
<td>0.77</td>
</tr>
<tr>
<td>prophylactic</td>
<td>45</td>
<td>45</td>
<td>0.95</td>
</tr>
<tr>
<td>angioplasty</td>
<td>5</td>
<td>1</td>
<td>0.10</td>
</tr>
<tr>
<td>aneurysm surgery</td>
<td>168</td>
<td>168</td>
<td>0.59</td>
</tr>
<tr>
<td>surgery on or after Day 7</td>
<td>15</td>
<td>8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Denominator for percentage calculation is the number of patients in each treatment group with complete data.

**TABLE 4**
Reasons for treatment termination due to adverse events

<table>
<thead>
<tr>
<th>Adverse Medical Event</th>
<th>Low-Dose Group</th>
<th>High-Dose Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>181</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>no. of terminations</td>
<td>18</td>
<td>10.0</td>
<td>17.9</td>
</tr>
<tr>
<td>reason for termination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypotension</td>
<td>6</td>
<td>3.3</td>
<td>6</td>
</tr>
<tr>
<td>renal dysfunction</td>
<td>3</td>
<td>1.7</td>
<td>4</td>
</tr>
<tr>
<td>pulmonary edema</td>
<td>6</td>
<td>3.3</td>
<td>10</td>
</tr>
<tr>
<td>liver dysfunction</td>
<td>1</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>arrhythmias</td>
<td>1</td>
<td>0.6</td>
<td>4</td>
</tr>
<tr>
<td>failed hypertension or relative hypotension</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>0.6</td>
<td>5</td>
</tr>
</tbody>
</table>

Neurological Change

Ischemic symptoms attributed to vasospasm were reported in 31.5% of low-dose and 31.0% of high-dose nicardipine-treated patients. The timing of the onset of symptoms was not significantly different between the groups (Fig. 1). Twelve patients in the high-dose group (7%) suffered the onset of symptomatic vasospasm following premature discontinuation of the study drug due to an adverse event, compared to six patients in the low-dose group (3%) (difference not significant). Neurological worsening occurred in 65 (36%) of low-dose and 62 (34%) of high-dose nicardipine-treated patients. The frequency of neurological worsening by primary or contributing cause after randomization was not significantly different between the groups (Table 5), except that 5% more patients in the low-dose group had worsening due to unknown causes (p = 0.05).

Arterial Narrowing

A total of 199 patients underwent transcranial Doppler ultrasound examinations between Days 7 and 11 (Table 6). Patients in the low-dose group were more likely to be female, and there was a trend toward more frequent use of antifibrinolytic drugs in the low-dose group. More patients in the low-dose group had mean MCA flow velocities above 120 cm/sec in each of three velocity groupings (Fig. 2), but the differences were not statistically significant.
TABLE 5

Frequency of any neurological worsening after randomization correlated with cause

<table>
<thead>
<tr>
<th>Cause of Worsening</th>
<th>Low-Dose Group*</th>
<th>High-Dose Group*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>181</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>initial bleed</td>
<td>15</td>
<td>11</td>
<td>0.39</td>
</tr>
<tr>
<td>vasospasm</td>
<td>32</td>
<td>31</td>
<td>0.83</td>
</tr>
<tr>
<td>rebleed</td>
<td>7</td>
<td>9</td>
<td>0.63</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>14</td>
<td>18</td>
<td>0.49</td>
</tr>
<tr>
<td>intracerebral hemorhage</td>
<td>3</td>
<td>4</td>
<td>0.72</td>
</tr>
<tr>
<td>surgery</td>
<td>11</td>
<td>17</td>
<td>0.26</td>
</tr>
<tr>
<td>hypotension</td>
<td>6</td>
<td>6</td>
<td>0.98</td>
</tr>
<tr>
<td>electrolyte level</td>
<td>5</td>
<td>5</td>
<td>1.00</td>
</tr>
<tr>
<td>unknown</td>
<td>16</td>
<td>7</td>
<td>0.05</td>
</tr>
<tr>
<td>other</td>
<td>34</td>
<td>31</td>
<td>0.63</td>
</tr>
</tbody>
</table>

* No. = number of patients with any event from that cause, primary or contributing.

TABLE 6

Characteristics of patients with transcranial Doppler ultrasound examinations performed between Days 7 and 11 following SAH*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-Dose Group†</th>
<th>High-Dose Group†</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age (yrs)</td>
<td>50.6 ± 14.7</td>
<td>51.2 ± 14.3</td>
<td>0.78</td>
</tr>
<tr>
<td>female</td>
<td>70</td>
<td>62</td>
<td>0.04</td>
</tr>
<tr>
<td>alert or drowsy</td>
<td>75</td>
<td>73</td>
<td>0.12</td>
</tr>
<tr>
<td>normal motor</td>
<td>71</td>
<td>71</td>
<td>0.26</td>
</tr>
<tr>
<td>hypertension</td>
<td>31</td>
<td>34</td>
<td>0.12</td>
</tr>
<tr>
<td>mean blood pressure</td>
<td>145.3 ± 24.1</td>
<td>148.7 ± 27.1</td>
<td>0.34</td>
</tr>
<tr>
<td>systolic</td>
<td>81.5 ± 12.6</td>
<td>83.7 ± 15.5</td>
<td>0.27</td>
</tr>
<tr>
<td>diastolic</td>
<td>14</td>
<td>14.7</td>
<td>0.11</td>
</tr>
<tr>
<td>antifibrinolytic drugs</td>
<td>28</td>
<td>29.8</td>
<td>0.41</td>
</tr>
<tr>
<td>intraventricular hematoma</td>
<td>83</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>clot on CT</td>
<td>22</td>
<td>32</td>
<td>0.66</td>
</tr>
<tr>
<td>diffuse thin</td>
<td>39</td>
<td>47.0</td>
<td>0.42</td>
</tr>
<tr>
<td>diffuse thick</td>
<td>9</td>
<td>10.8</td>
<td>0.72</td>
</tr>
<tr>
<td>localized thin</td>
<td>13</td>
<td>15.7</td>
<td>0.17</td>
</tr>
<tr>
<td>localized thick</td>
<td>13</td>
<td>15.7</td>
<td>0.17</td>
</tr>
</tbody>
</table>

* SAH = subarachnoid hemorrhage; CT = computerized tomography. Mean values are expressed ± standard deviation. † Total = number with available data; No. and % = number and percent with indicated prognostic factor.

Follow-up cerebral angiography was performed in 17% of patients in the low-dose group between Days 7 and 11 following SAH, compared to 24% of patients in the high-dose group (p = 0.11). A greater (although not statistically significant) proportion of patients without symptoms of vasospasm had follow-up angiography in the high-dose group (17% vs. 12%), while the proportion of patients with symptomatic vasospasm who underwent angiography was more similar in the two groups (7% in the high-dose group vs. 5% in the low-dose group). Among patients with angiography performed between Days 7 and 11, the baseline characteristics and prognostic factors for vasospasm were not significantly different between the groups, except that a greater proportion of low-dose nicardipine-treated patients were female (Table 7). In the low-dose group, 39% had moderate or severe angiographic vasospasm versus 19% in the high-dose group (p = 0.08) (Fig. 3).

Clinical Outcome

At follow-up evaluation, which ranged from 3 to 411 days (median 100 days in the low-dose group, 96 days in the high-dose group), overall outcome as assessed using the GOS was similar in both groups (Fig. 4). A good recovery was achieved in 59% of patients in the low-dose group and 12% died, while 58% of patients in the high-dose group made a good recovery and 11% died. The causes of death and disability are shown in Table 8. While there were no statistically significant differences in the primary causes of death and disability, vasospasm was cited more frequently as a primary or contributing cause of death or disability in the low-dose group than in the high-dose group (12.5% vs. 5.7%, p = 0.03).

The NIH Stroke Scale and Mini-Mental State scores were not significantly different in survivors at follow-up examination (Table 9). Seventy-two (56%) of 128 low-dose and 73 (59%) of 124 high-dose nicardipine-treated patients had cerebral infarctions detected on follow-up CT scans. The volumes of the measured infarctions were not significantly different between the groups, and the prognostic factors for vasospasm were balanced between the groups in the subset of patients who underwent follow-up CT. Among those patients who had infarcts detected, the median infarct

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TABLE 7
Characteristics of patients with follow-up angiography performed between Days 7 and 11 post-SAH*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-Dose Group†</th>
<th>High-Dose Group‡</th>
<th>( \bar{p} ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases with angiograms</td>
<td>181 31</td>
<td>184 44</td>
<td>23.9 0.11</td>
</tr>
<tr>
<td>female</td>
<td>31 23</td>
<td>44 21</td>
<td>47.7 0.02</td>
</tr>
<tr>
<td>alert or drowsy</td>
<td>30 26</td>
<td>44 37</td>
<td>84.1 1.00</td>
</tr>
<tr>
<td>normal motor</td>
<td>30 28</td>
<td>44 35</td>
<td>79.6 0.18</td>
</tr>
<tr>
<td>hypertension</td>
<td>29 8</td>
<td>43 14</td>
<td>32.6 0.65</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>31 52.5 ± 15.4</td>
<td>44 49.9 ± 16.6</td>
<td>0.48</td>
</tr>
<tr>
<td>mean blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>31 142.5 ± 21.3</td>
<td>44 148.0 ± 30.8</td>
<td>0.37</td>
</tr>
<tr>
<td>diastolic</td>
<td>31 79.8 ± 13.0</td>
<td>44 82.5 ± 16.7</td>
<td>0.44</td>
</tr>
<tr>
<td>antifibrinolytic drugs</td>
<td>31 3 9.7</td>
<td>44 1 2.3</td>
<td>0.30</td>
</tr>
<tr>
<td>clot on CT</td>
<td>25 6</td>
<td>39 10</td>
<td>25.6 0.48</td>
</tr>
<tr>
<td>diffuse thin</td>
<td>14 36.0</td>
<td>15 38.5</td>
<td></td>
</tr>
<tr>
<td>diffuse thick</td>
<td>2 8</td>
<td>4 10</td>
<td>10.3</td>
</tr>
<tr>
<td>localized thin</td>
<td>3 12.0</td>
<td>10 25.6</td>
<td></td>
</tr>
<tr>
<td>localized thick</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intraventricular hemorraghe</td>
<td>30 6</td>
<td>43 11</td>
<td>25.6 0.58</td>
</tr>
</tbody>
</table>

* SAH = subarachnoid hemorrhage; CT = computerized tomography.
† Total = number with available data; No. and % = number and percent with indicated characteristic. Mean values are expressed ± standard deviation.
‡ Fisher's exact test.

volume was 9.1 cc in the low-dose group and 12.3 cc in the high-dose group (not significant).

Complications

The incidence of over 50 medical and neurological complications was monitored during the study. The incidence of hypotension, defined as a systolic blood pressure of less than 100 mm Hg, was not significantly different between the groups, occurring in 28% of patients in the low-dose group and 33% of patients in the high-dose group. Severe hypotension, that is, life-threatening with symptoms of end organ ischemia, occurred in 0.6% of low-dose and 1.1% of high-dose nicardipine-treated patients. Mean systolic and diastolic blood pressures were not significantly different between the groups on any day during treatment. Relative hypotension, defined as a systolic blood pressure that fell below baseline, but not to less than 100 mm Hg, was reported with similar frequency in both groups (8% in the low-dose group vs. 10% in the high-dose group, \( p = \) not significant), and the inability to induce therapeutic hypertension (failed hypertension) was also reported similarly in both groups (6% in the low-dose group vs. 5% in the high-dose group, \( p = \) not significant). The incidence of renal dysfunction was 13% in the low-dose group and 16% in the high-dose group (\( p = \) not significant). Phlebitis at the injection site was reported in 14% of patients in the high-dose group compared to 8% of low-dose nicardipine-treated patients (\( p = 0.11 \)).

Pulmonary edema was reported in 34% of high-dose compared to 20% of low-dose nicardipine-treated patients, a statistically significant difference (\( p < 0.01 \)). Pulmonary edema was judged to be severe or life-threatening in 0.5% of patients in the high-dose group versus 1.7% of patients in the low-dose group. The only other complication reported at significantly different rates was the syndrome of inappropriate antidiuretic hormone secretion, which was reported more frequently in the low-dose group (6% vs. 1%, \( p < 0.05 \)).

FIG. 3. Bar graph showing the severity of vasospasm in patients with follow-up cerebral angiograms obtained between Days 7 and 11 following subarachnoid hemorrhage. A greater proportion of patients in the high-dose group had no detectable angiographic vasospasm, and the differences in the overall distributions were statistically significant (\( p < 0.05 \), Fisher's exact test).

FIG. 4. Bar graph illustrating the overall outcomes as determined using the Glasgow Outcome Scale in all patients randomly assigned to treatment with either low-dose or high-dose nicardipine. There were no statistically significant differences in any of the outcome strata.

Discussion

The results of this randomized dosing study of the dihydropyridine calcium antagonist nicardipine sug-
TABLE 8
Primary and contributing causes of death and disability*  

<table>
<thead>
<tr>
<th>Cause</th>
<th>Low-Dose Group</th>
<th>High-Dose Group</th>
<th>( p ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death No. %</td>
<td>Disabled No. %</td>
<td>Totals (%)</td>
</tr>
<tr>
<td>no. of cases</td>
<td>176</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>lost to follow-up review</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>direct effect</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary vasospasm</td>
<td>28</td>
<td>15.9</td>
<td>18.8</td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary ischemia/other cause</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rebled</td>
<td>2</td>
<td>1.1</td>
<td>2.8</td>
</tr>
<tr>
<td>primary hemorrhage</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgical complication</td>
<td>1</td>
<td>4.0</td>
<td>5.1</td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medical therapy</td>
<td>1</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intracerebral hemorhage</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary &amp; contributing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>totals</td>
<td>22</td>
<td>25.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>

* Disability is defined as any outcome other than good recovery or death according to the Glasgow Outcome Scale.†
‡ NS = not statistically significant.
§ Fisher's exact test.

TABLE 9
Neurological and radiological outcome at follow-up review

<table>
<thead>
<tr>
<th>Examination &amp; Treatment Group*</th>
<th>No. of Cases</th>
<th>Findings</th>
<th>Minimum 25th Percentile</th>
<th>Median</th>
<th>75th Percentile</th>
<th>Maximum</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Stroke Scale score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low dose</td>
<td>124</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>19</td>
<td>0.53‡</td>
<td></td>
</tr>
<tr>
<td>high dose</td>
<td>125</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low dose</td>
<td>126</td>
<td>0</td>
<td>27</td>
<td>30</td>
<td>30</td>
<td>0.67‡</td>
<td></td>
</tr>
<tr>
<td>high dose</td>
<td>121</td>
<td>0</td>
<td>27</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT infarct volume (cc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low dose</td>
<td>128</td>
<td>0</td>
<td>0.9</td>
<td>10</td>
<td>447</td>
<td>0.28‡</td>
<td></td>
</tr>
<tr>
<td>high dose</td>
<td>124</td>
<td>0</td>
<td>1.8</td>
<td>18</td>
<td>230</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CT = computed tomography.
† Eleven patients in the low-dose group and 16 patients in the high-dose group had incomplete, missing, or untestable tests in their National Institutes of Health (NIH) Stroke Scale examinations, and are not included in this analysis.
‡ Krukal-Wallis test.

gest that 0.075 mg/kg/hr by continuous intravenous infusion is better tolerated in patients with recent aneurysmal SAH than the high dose of 0.15 mg/kg/hr. Adjustment of the results by sex did not alter any of the conclusions. The incidence of symptomatic vasospasm and the overall clinical outcome were virtually identical with either dose regimen. As with any small study showing no significant differences, a type 2 statistical error cannot be excluded, but the sample size is robust enough to generate power in excess of 80% for detecting an absolute 15% increase in symptomatic vasospasm in the low-dose group, if it really existed. Therefore, it seems unlikely that any clinically important differences in outcome exist between the two dosing schemes. Similar power exists for detection of differences in complication rates.

The mechanism underlying the association between high-dose nicardipine and pulmonary edema remains uncertain. Perhaps this represents a form of "high-output" pulmonary edema produced by the profound lowering of systemic vascular resistance attending
Nicardipine dose comparison in aneurysmal SAH

Nicardipine administration in some patients. In any event, the evidence is strong that intravenous nicardipine may be associated with this complication, and prompt recognition and appropriate dosage modifications may be lifesaving in some cases.

The results of this study are remarkably consistent with the results of the placebo-controlled trial of intravenous nicardipine in SAH reported previously. The incidence of symptomatic vasospasm observed with either dose of nicardipine tested in this study (31% to 32%) is similar to the rate reported in the nicardipine group in the previous trial (31.6%), which was clearly lower than the rate reported in the placebo-treated group (45.5%). Of note is the finding that the mortality rate in both groups in the present study (11.5%) was better than that in the high-dose nicardipine group in the placebo-controlled trial (17%) (p < 0.01). As the patients appeared to be similar at baseline, the reasons for the apparent improvement in the mortality rate in the present study are not clear.

One question not completely settled by the observation in this trial is whether there is a difference in the incidence or severity of arterial narrowing between the two dosage groups. Flamm and colleagues, in their open dose-escalation trial, observed a significant reduction in angiographic vasospasm with administration of nicardipine at a dose of 0.15 mg/kg/hr compared to lower doses. However, patients in that trial were not randomly assigned to dosage groups. In the current study, selection bias, as evidenced by the difference in proportions between the groups of patients with angiograms performed on Days 7 to 11 and the tendency for more asymptomatic patients in the high-dose group to be studied, may have at least partially accounted for the observation of more angiographic vasospasm in the low-dose group. The sample sizes are larger for the ultrasound study data, and the apparent differences in the incidence and severity of vasospasm are smaller and not statistically significant.

Even if there is a dose-dependent difference in angiographic vasospasm, it is not apparent clinically. There was no difference in either the incidence or severity (as determined by daily neurological examinations) of ischemic deficits from vasospasm observed during hospitalization, and the incidence and volume of measured CT infarction were nearly the same at follow-up evaluation. Vasospasm was cited more frequently as a contributing cause of disability at follow-up review in the low-dose group, but attribution of the cause of disability in this critically ill population of patients is notoriously difficult.

Conclusions

These observations suggest that nicardipine at a dose of 0.075 mg/kg/hr via continuous intravenous infusion is better tolerated and may be as effective as administration at a dose of 0.15 mg/kg/hr in patients with aneurysmal SAH. From a practical standpoint, the ability to titrate the dose of nicardipine to individual tolerance (watching for hypotension, renal dysfunction, and pulmonary edema) makes it a potentially very useful drug in the management of these critically ill patients.

APPENDIX

Participants in the Study

Clinical centers participating in this study:

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