Hemoglobin Concentration and Prognosis in Symptomatic Obstructive Cerebrovascular Disease

for the EC/IC Bypass Study Group

A total of 1,377 patients with symptomatic obstructive cerebrovascular disease (most commonly, internal carotid artery occlusion) entered a trial in which they were randomized to either medical or surgical (extracranial–intracranial bypass) therapy. All but 8 had hemoglobin estimations performed at entry. The patients were followed for an average of 55.8 months. In the medical group, the 325 patients with high normal hemoglobin concentration (15 g/l or more) suffered no more ischemic strokes than the 382 patients with lower values (<15 g/l). Those strokes that did occur were no more severe in the high than the low hemoglobin group. Hemoglobin concentration did not emerge as a prognostic factor in those patients treated surgically (n = 662). This prospective study counters the hypothesis that high normal hemoglobin concentration is associated with poor outcome in patients with symptomatic obstructive disease of the carotid and cerebral arteries. 

DATA from the Framingham survey1 have suggested that a high hemoglobin concentration (>15 g/l in men and 14 g/l in women) is a risk factor for cerebral infarction. In a Japanese necropsy study,2 the extent of cerebral atherosclerosis and the value of the hematocrit (Hct) in combination were strong predictors of the presence and extent of cerebral ischemic lesions. The volume of cerebral infarction as estimated by computerized tomography (CT) scan has been correlated with Hct in patients presenting with stroke from angiographically confirmed carotid occlusion.3 In these latter two studies, Hct may have been measured shortly after cerebral infarction, a time when other variables, such as dehydration and sympathetic drive, can lead to a temporary increase in value.

The EC/IC Bypass Study Group4–3 data base offers a unique opportunity to assess prospectively the predictive role of hemoglobin concentration on clinical outcome in patients with symptomatic obstructive carotid and intracranial arterial disease. It forms the basis of the present study.

Subjects and Methods

The EC/IC Bypass Study was a randomized trial designed to determine whether extracranial–intracranial (EC–IC) bypass surgery reduced the subsequent incidence of stroke and/or stroke-related death in patients with symptomatic but inaccessible stenosis or occlusion of the internal carotid (ICA) or middle cerebral arteries (MCA). The methodology and entry characteristics have been fully described elsewhere.4 The following is a brief summary of methodology relevant to this paper. Poor functional status excluded patients from the trial, and 93% had either minimal or no functional impairment at entry although 74% had some abnormality on neurological examination. Bilateral carotid angiograms on all patients were available, and a hemoglobin estimation was performed as part of the initial assessment. Follow-up examination, performed by the participating neurologist, was undertaken 6 weeks after randomization and at 3-month intervals thereafter.

No patient was lost, and none were withdrawn from followup. The average duration of followup for surviving patients (medical and surgical) was 55.8 months (range 28–90). Acetylsalicylic acid (325 mg q.i.d.) was prescribed for all patients throughout the trial unless contraindicated, and the control of hypertension was encouraged and monitored centrally.

The main study endpoints were postrandomization fatal and nonfatal stroke of all types, but subdivision into ischemic and hemorrhagic stroke was also undertaken using the best available means (usually CT scan). The severity of stroke in terms of functional impairment was rated on an 11-point scale ranging from no impairment with signs and/or symptoms only (1–3), through minor impairment (4–9), to a variable loss of independence (5–9), depressed consciousness (10), and death (11).4 All endpoints were adjudicated by a nonparticipating neurologist and neurosurgeon.

A total of 1,377 patients entered the trial. Of the 714 patients randomized to the medical group, initial hemoglobin estimations were available on 707. Of these, 419 were randomized for ICA occlusion, 118 for ICA stenosis, 115 for tandem ICA and MCA lesions, and 55 for MCA lesions alone. The surgical group comprised 662 patients, and the hematological data were missing in 1 case. Randomization created comparable groups with respect to underlying vascular pathology and concomitant risk factors.

In the present study, the primary analysis compares the occurrence of all fatal and nonfatal ischemic
strokes (including retinal) in the medically treated group at various hemoglobin levels using the Mantel-Haenszel χ² statistic. We have also analyzed the occurrence of fatal and nonfatal ischemic strokes in the surgical group to see if high normal hemoglobin is a predictor of poor outcome.

Results

Hemoglobin Concentration and Entry Characteristics

The hemoglobin concentration was available on 1,369 of the 1,377 patients who entered the EC/IC Bypass Study. Of these, 912 were randomized for stroke (many of whom had TIA’s as well), and 457 had only TIA’s. The mean ± SD for the group with stroke was 14.6 ± 1.6 g/1 and for the TIA group 14.7 ± 1.7 g/1. The hemoglobin concentration bore no relation to the functional status of the patients at entry. Thus, patients with high normal hemoglobin values had no more strokes and were not more disabled at entry into the trial than patients with similar vascular disease and lower hemoglobin values.

Hemoglobin Concentration and Outcome in the Medical Group

We initially divided the medical group (n = 707) into 3 subgroups based on the hemoglobin level at entry: < 14 (n = 206), 14–16 (n = 381), and > 16 g/1 (n = 120). The 3 subgroups fared similarly with respect to the incidence of all ischemic strokes occurring during followup.

For comparison with the Framingham study, the data were then analyzed using a cutoff hemoglobin value of 15 g/1. Of the 707 patients, 382 had a hemoglobin concentration < 15 g/1 and 325 of 15 g/1 or more. Again, the endpoints were considered to be all fatal and nonfatal ischemic strokes. The results are shown in Table 1. A trend emerged in which patients with higher hemoglobin levels suffered fewer strokes, but this result did not achieve statistical significance.

Of the 707 patients in the medical group, 579 (82%) were men. A separate analysis among males again showed a nonsignificant trend favoring patients with higher hemoglobins.

An analysis of fatal and nonfatal ischemic strokes among the 419 medical patients randomized for ICA occlusion showed no significant difference in stroke frequency between lower (< 15 g/l) and higher (15 g/l or more) hemoglobin groups (Table 1). Of these 419 patients, 147 continued to have recurrent symptoms after the occlusion had been angiographically confirmed. Among these patients, those with higher hemoglobin levels again tended to do better.

Potentially confounding concomitant risk factors (age, male sex, hypertension, diabetes, smoking status, cholesterol levels) occurred with equal frequency in patients with a hemoglobin concentration of < 15 g/l and in those with levels of 15 g/l or more.

We next considered the severity of the first ischemic stroke in all medical patients who had suffered an ischemic stroke (n = 191). For this analysis, stroke severity was assessed using the EC–IC stroke severity scale. A comparison of initial hemoglobin concentrations among the 11 stroke severity subgroups revealed no association between the severity of the lesion and the prior evaluation of hemoglobin concentration (Table 2).

Hemoglobin Concentration and Outcome in the Surgical Group

Of the 663 patients randomized to surgical treatment, 662 had hemoglobin estimations at entry. The value was < 15 g/1 in 376 and 15 g/1 or more in 286 subjects. Analysis of outcome using all fatal and nonfatal ischemic strokes failed to demonstrate any difference in the two groups, although here the trend was in the opposite direction to the medical group, with the low-hemoglobin group doing better than those with higher values.

Table 1. Number of Patients With Fatal and Nonfatal Ischemic Stroke in Low- and High-Hemoglobin Groups

<table>
<thead>
<tr>
<th>Patients</th>
<th>Low-Hemoglobin group</th>
<th>High-Hemoglobin group</th>
<th>Mantel-Haenszel χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 15 g/l</td>
<td>Strokes observed</td>
<td>Strokes expected</td>
</tr>
<tr>
<td>All patients randomized to medical group (N = 707)</td>
<td>382</td>
<td>111</td>
<td>101</td>
</tr>
<tr>
<td>Male patients randomized to medical group (N = 579)</td>
<td>275</td>
<td>82</td>
<td>71</td>
</tr>
<tr>
<td>Patients with ICA occlusion randomized to medical group (N = 419)</td>
<td>218</td>
<td>64</td>
<td>58</td>
</tr>
<tr>
<td>Patients with ICA occlusion and recurrent symptoms randomized to medical group (N = 147)</td>
<td>73</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>All patients randomized to surgical group (N = 662)</td>
<td>376</td>
<td>103</td>
<td>112</td>
</tr>
</tbody>
</table>

Low-Hemoglobin group (mean ± SD) 13.5 ± 1.2; High-Hemoglobin group 16.0 ± 0.9.

ICA, internal carotid artery.
Table 2. Entry Hemoglobin by Severity of the First Ischemic Stroke Following Randomization Among Patients Randomized to Medical Treatment

<table>
<thead>
<tr>
<th>Stroke severity scale</th>
<th>n</th>
<th>Mean g/l</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Neurological signs only</td>
<td>10</td>
<td>14.6</td>
<td>1.2</td>
<td>12.7-16.4</td>
</tr>
<tr>
<td>2. Neurological symptoms only</td>
<td>1</td>
<td>17.4</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>3. Signs and symptoms</td>
<td>42</td>
<td>15.0</td>
<td>1.4</td>
<td>11.9-18.3</td>
</tr>
<tr>
<td><strong>Minor impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. In any domain*</td>
<td>75</td>
<td>14.5</td>
<td>1.5</td>
<td>11.5-17.5</td>
</tr>
<tr>
<td><strong>Major impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. In 1 domain</td>
<td>17</td>
<td>14.3</td>
<td>1.4</td>
<td>10.9-16.7</td>
</tr>
<tr>
<td>6. In 2 domains</td>
<td>19</td>
<td>14.1</td>
<td>2.5</td>
<td>7.9-17.6</td>
</tr>
<tr>
<td>7. In 3 domains</td>
<td>5</td>
<td>12.9</td>
<td>2.3</td>
<td>10.1-1.54</td>
</tr>
<tr>
<td>8. In 4 domains</td>
<td>5</td>
<td>14.5</td>
<td>0.9</td>
<td>13.4-15.9</td>
</tr>
<tr>
<td>9. In 5 domains</td>
<td>1</td>
<td>17.1</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>10. Reduced consciousness</td>
<td>4</td>
<td>15.3</td>
<td>0.5</td>
<td>14.8-15.8</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Death</td>
<td>12</td>
<td>14.8</td>
<td>1.0</td>
<td>12.7-16.2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>191</td>
<td>14.6</td>
<td>1.6</td>
<td>7.9-18.3</td>
</tr>
</tbody>
</table>

*Impairments include difficulty in function (minor) or inability to function without assistance (major) in the following domains: communication, comprehension, swallowing, self-care, and ambulation.

Discussion

The results of the present study clearly show that patients with high hemoglobin concentrations and symptomatic obstructive cerebrovascular disease fare no worse than those with lower values. They do not suffer more ischemic strokes, and those strokes that do occur are no more severe than in subjects with low hemoglobin and equivalent vascular pathology. Indeed, there was a trend, albeit not statistically significant, which suggested the reverse in the medically treated group. The cutoff point for the analysis, at 15 g/l, is somewhat arbitrary, but it was chosen because the Framingham data suggest that men with values of 15 g/l or greater and women with levels of 14 g/l or more suffer twice as many cerebral infarctions as do patients with lower values. While the conclusions drawn from the present study and the Framingham survey appear contradictory, the difference in patient populations deserves consideration, and it is worth emphasizing how patients were deemed eligible for the EC–IC trial. An essential prerequisite was that they had all survived severe obstructive episodes (usually ICA occlusion) with either minimal or mild residual signs. This attests to the efficiency of their collateral circulation, and they cannot be considered representative of the clinical spectrum of severe occlusive vascular disease in general. They are also very different from the patients described in the study by Harrison et al., which considered only patients with CT-proven infarction as a consequence of ICA occlusion. What we have shown is that in a prospective study, the initial hemoglobin concentration has no bearing on outcome in subjects who have survived an occlusive episode without major disability. The same holds true for those patients who underwent EC–IC bypass surgery.

The rheological ramifications are intriguing. Cerebrovascular disease (CBF) is low in patients with high hemoglobin, but returns to normal once the hemoglobin has been lowered by venesection. This may be because of the resultant reduction in blood viscosity, but in subjects with normal vessels a more likely explanation is the secondary fall in the arterial oxygen-carrying capacity since the product of CBF and arterial oxygen content remains relatively stable. Rheological factors should become more important, however, when the arteries are severely diseased since the compensatory reserve of the microcirculation for further vasodilation may be exhausted. Patients with delayed TIA's and proven ICA occlusion may thus show a blunted response to potent cerebral vasodilators such as 5% carbon dioxide inhalation. When the microcirculation is maximally dilated, CBF will be dictated by the pressure gradient across the circulation and the viscosity of the blood. Hct (and hence hemoglobin concentration) is the single most important factor governing blood viscosity when studied in vitro in relatively large-bore viscometers. If a large proportion of patients in the present study were hemodynamically compromised, then we would expect those with higher hemoglobin values and hence higher viscosity to fare worse. This did not emerge even in those patients with ICA occlusion and recurrent ischemic events. It is also worth pointing out that this subgroup did poorly following bypass surgery; in the primary analysis they fared worse with surgery than with medical therapy ($\chi^2 = 4.04$). There may be an association between high Hct and carotid occlusion, and the risk of thrombosis appears related to the value of Hct, at least in patients with polycythemia rubra vera. Our study neither supports...
nor refutes these findings. But once occlusion has occurred, hemoglobin concentration has no bearing on delayed symptoms, which suggests that few are of hemodynamic origin. Recurrent thromboembolism via collateral channels seems the probable explanation, and antithrombotic therapy rather than Hct reduction appears the more logical therapy.

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**References**


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