Recovery of Cognitive Function After Surgery for Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—Abnormalities in neurocognitive function are common after surgery for aneurysmal subarachnoid hemorrhage, even among patients with good functional outcomes. The time course of neurocognitive recovery, along with the long-term effects of mild intraoperative hypothermia (33°C) and aneurysm location, is unknown. We determined these in a subset of subarachnoid hemorrhage patients enrolled in the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST).

Methods—We performed a longitudinal, multicenter, prospective, blinded study of adult IHAST patients with a Glasgow Outcome Score=1 or 2 (independent function), 3 months postsurgery and a matched control group (n=45). Subjects were tested with a 5-test cognitive function battery and standard neurological evaluations at 3, 9 and 15 months postsurgery. The primary outcome measure was a composite score on cognitive test performance.

Results—There were 303 IHAST patients available for inclusion: 218 eligible, 185 enrolled (89 hypothermic, 96 normothermic). Significant cognitive improvement was noted from 3 to 9 (P<0.001) and 3 to 15 (P<0.001) months in both hypothermic and normothermic groups, even after adjusting for practice effects observed in the control group. No significant change was identified between 9 and 15 months. Neither mild hypothermia nor aneurysm location (anterior communicating artery versus others) had a significant effect on recovery over time or frequency of cognitive impairment. Compared with control group, the frequency of cognitive impairment (Z score < −1.96) in all patients at 3, 9 and 15 months was 36%, 26% and 23%, respectively.

Conclusions—In this population, cognitive improvement continued beyond 3 months, with a plateau between 9 and 15 months. This was not affected by the use of intraoperative hypothermia or anatomical location of aneurysm. (Stroke. 2007;38:1864-1872.)

Key Words: clinical trial ■ cognitive function ■ intracranial aneurysm ■ neuropsychological testing ■ subarachnoid hemorrhage

Abnormalities in neurocognitive function are common after subarachnoid hemorrhage (SAH) and surgery for aneurysmal SAH, even among patients with otherwise good functional outcomes. Among patients assessed as having “good outcomes” using the Glasgow Outcome Scale (GOS), 60% or more have abnormalities in 1 or more neurocognitive domains1−5 with assessments made relatively soon (3 to 6 months) after the initial hemorrhage. Although measurements at longer intervals have been made, the data regarding long-term longitudinal/serial assessments of neuropsychological performance after SAH are limited.

The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was designed to determine the influence of mild intraoperative cooling of patients with acute SAH on neurological outcome 3 months after treatment. This study found no difference in the incidence of “good outcomes” on multiple measures of neurological functional outcome including the GOS, Rankin Disability Scale, the National Institutes of Health Stroke Scale (NIHSS) and the Barthel Activities of Daily Living scale. IHAST also assessed neurocognitive function 3 months postsurgery with 5 standard neuropsychological tests, which also failed to...
demonstrate any effect of intraoperative hypothermia.\textsuperscript{5} This provided, however, the opportunity to longitudinally evaluate long-term patterns of neurocognitive behavior in the study population.

The Cognitive Function After Aneurysm Surgery Trial (CFAAST) was therefore designed as a longitudinal, ancillary study to IHAST. The specific aims of CFAAST were to evaluate: (1) the incidence and severity of cognitive dysfunction among IHAST patients with “good” neurological outcome, (2) the time course of recovery of cognitive function after SAH, and (3) the effects of aneurysm location and mild intraoperative hypothermia on cognitive function over time.

Methods

CFAAST is an international, multicenter, prospective, blinded, longitudinal study of patients enrolled in IHAST with an additional recruited control group matched to IHAST patients enrolled before November 2002 (start date for CFAAST) for age, racial phenotype, gender and education.

Study Population

IHAST Patients

IHAST was a prospective, randomized, clinical trial with outcome assessments made by blinded examiners. Details of the trial, eligibility criteria, randomization, treatment protocols and outcome measures have been previously described.\textsuperscript{4} Briefly, the trial was designed to determine the impact of mild intraoperative hypothermia on outcome in patients with acute SAH who underwent craniotomy and aneurysm clipping within 14 days of hemorrhage. IHAST patients were nonobese (BMI \textless{}35), nonpregnant, adults with angiographically proven SAH and a preoperative World Federation of Neurologic Surgeons score of I, II or III (WFNS I\textsuperscript{=}, Glasgow Coma Score [GCS] score 15, no motor deficit; WFNS II\textsuperscript{=}, GCS score 13 or 14, no motor deficit; WFNS= GCS score 13 or 14, any motor deficit). Patients were randomized, after induction of anesthesia, to either hypothermic (temperature=32.5\degree{} to 33.5\degree{}) or normothermic (temperature=36\degree{} to 37\degree{}) groups, with the goal of achieving target temperature by the time of first clip application. Aneurysm location was determined preoperatively by cerebral angiogram.

CFAAST Patients

The target population for CFAAST was IHAST patients who met the following additional eligibility criteria: (1) good outcome or moderate disability, as defined by a GOS of 1 or 2, 3 months after surgery. Patients with GOS \textgreater{}3 were excluded (with the exception of a single patient who had GOS=3 at 3 months but improved to GOS=2 when seen on a routine clinic visit, 6 months after surgery) because the extent of disability would have made it hard for them to undergo planned cognitive testing; (2) ability to read and comprehend English language adequately to complete cognitive function testing; and (3) expected availability for follow-up visits at 9 and 15 months postsurgery. Patients in whom an elective neurosurgical procedure was planned within the 15-month interval after craniotomy (eg, patients scheduled to undergo clipping of an unruptured aneurysm discovered at the time of their IHAST enrollment) were excluded.

CFAAST Recruitment

IHAST centers enrolled 1001 patients between February 2000 and April 2003. All 25 IHAST centers active in November 2002 (start of CFAAST) were invited to participate with 21 of 25 centers joining CFAAST. Following local Institutional Review Board/ethics committee approval, all eligible patients were contacted regarding participation. We recruited a control group of 45 subjects from a convenience sample of southeastern Michigan residents using print advertising. These individuals had no known central nervous system disease by review of past medical history and medications, and were actively matched for age, racial phenotype, gender and education level to patients enrolled in IHAST before November 2002. Written informed consent was obtained from all subjects enrolled in CFAAST.

Cognitive and Functional Assessment

IHAST

The purpose of cognitive evaluation in IHAST was to provide a standardized, quantitative index of outcome in the key domains of global cognition, memory, language, visuospatial abilities, attention and executive functioning. This was assessed by trained neuropsychologists using a battery of 5 tests: the Benton Visual Retention Test-Revised (BVRT-R),\textsuperscript{6} the Controlled Oral Word Association (COWA),\textsuperscript{7} the Grooved Pegboard Test (GPT),\textsuperscript{8} the Rey-Osterreith Complex Figure Test-Copy (CFT)\textsuperscript{9} and the Trail making Test A & B (TMT).\textsuperscript{9} This battery of tests was selected based on prior analysis of data from a comprehensive neuropsychological evaluation (using 15 to 30 individual tests) given to a group of 94 survivors of subarachnoid hemorrhage. The panel of tests above demonstrated 95\% agreement with the results of the comprehensive neuropsychological evaluation in assessing the presence or absence of cognitive impairment (Dr Steven Anderson, unpublished data: Patient Registry of the Division of Cognitive Neuroscience in the Department of Neurology at the University of Iowa, 1995).

Neurological function in IHAST was measured using the GOS, Rankin Disability Scale, Barthel Activities of Daily Living Index, and the NIHSS administered by trained study personnel. All assessments were made by research personnel blinded to IHAST treatment group assignment.

CFAAST

For CFAAST, 2 tests were added to the IHAST cognitive battery to assess premorbid intellectual function and symptoms of depression. Specific tests used were the National Adult Reading Test–Revised (NART-R),\textsuperscript{5,10} and the Beck Depression Inventory-II (BDI-II).\textsuperscript{11,12} CFAAST patients also underwent serial neurological function assessments using the same measures and process described above for IHAST.

All cognitive testing in CFAAST was conducted by a certified neuropsychologist or a supervised psychometrician with a minimum of 1-year experience in administering neuropsychological tests. Standardized cognitive testing materials and instructions were provided to all participating centers and examiners blinded to IHAST treatment group. All data were sent to the data management center for scoring and analyses. All control subjects were examined by, or under the supervision of, the same neuropsychologist (A.F.C.).

Timing of Assessments

CFAAST patients were assessed 9 and 15 months postsurgery using the entire test battery with the exception of the NART-R, which was administered at 15 months only. IHAST 3-month outcome assessments formed the baseline for CFAAST patients. Control subjects were examined at baseline, 6 and 12 months.

Cognitive Test Scoring

The University of Iowa served as the Data Management Center. After neuropsychological and behavioral tests were administered, the data were independently double-scored by 2 trained technicians, each working under the supervision of a neuropsychologist. All 4 individuals were blinded to group assignment or other outcome assessments. Scoring discrepancies were resolved between the 2 scoring teams. Raw test scores were converted to \textit{t} scores based on normative data from the following published sources (test-data source): BVRT-Sivan,\textsuperscript{14} COWA-Benton,\textsuperscript{15} CFT-Wefel (Wefel JS, Boward KE, unpublished data, 1995), TMT-Heaton,\textsuperscript{17} GPT-Heaton.\textsuperscript{17}

\textit{t} scores for BVRT (number correct), COWA (letters CFL at 3 & 15 and PRW at 9-month visit), CFT, GPT (time to completion) and TMT A & B (time to completion) were then averaged with equal weighting to provide a composite score for each patient. Use of a composite score minimizes floor and ceiling effects on test scores.
and the risk of Type I error when multiple performance domains are used, as well as increasing sensitivity to finding generalized, subtle change over time when heterogeneity in cognitive domain impairment and recovery rates are expected.18,19

The composite score provided an index of overall cognitive status for each patient. For subjects completing only 3 or 4 elements of the cognitive test battery, the composite score was computed using the averaged data from the completed tests. Neuropsychological scoring for IHAST and CFAAST were completely separate. Each group worked with coded raw test forms, without consultation between centers. All neuropsychological results presented here are the product of the CFAAST investigative team. No effort was made to reconcile scoring differences between IHAST and CFAAST.

**Statistical Analyses**

All analyses were performed using SAS under the guidance and supervision of one of the investigators (W.R.C.). As a first step, age, education and the NART-R score were treated as continuous independent variables and analyzed to identify significant differences in their distributions between the hypothermia and normothermia treatment groups or between anatomical locations of aneurysms (anterior communicating versus all other locations).

Comparisons of baseline characteristics of the treatment groups and between treated patients and controls used χ2 tests for categorical variables and Kruskal-Wallis nonparametric tests for continuous variables. Linear mixed models were used to examine the effects of treatment group, aneurysm location, and time since surgery on composite score. The NART-R score and age were included as covariates because inspection of the distribution of age, education and NART-R score across the groups by the hypothermia and normothermia and aneurysm location (anterior communicating artery and all other locations) revealed that only age and NART-R score approached statistical significance in some of the cells. The models had terms for 2- and 3-way interactions between treatment, location and time of testing (3, 9 and 15 months) and assumed an unstructured correlation matrix. Adjusted (least squares) means were calculated using these models.

Two methods, using data from the control group, were used to adjust for possible learning effects attributable to repeated testing. These methods convert each observed value of composite score to a Z statistic and then adjust for change in performance observed in control group. For cross-sectional comparisons (method A), separate adjustments using control group data were done for 3, 9 and 15 months. For comparisons of change in scores (9- and 15-month performance to 3 months), comparable change values over time in control group were used (method B). Method A used the formula:

\[
Z = \frac{\text{Observed} - \text{Control}}{\text{SD (Control)}}
\]

and method B used the formula:

\[
Z = \frac{\sum \text{Observed} - \sum \text{Controls}}{\text{SD (Controls)}}
\]

In these formulae, Z is the adjusted score, 'Observed' is the observed composite score, 'Control' is the mean and 'SD (Control)' is the standard deviation computed for the control group only, and \( \Delta \) represents the change from 3 months (9 or 15 months–3 months). Statistical analyses of observed Z scores used the same mixed model approach that was used for the unadjusted means.

A third approach (method C) was also used to determine the frequency of cognitive impairment. In this case, based on recommendations from the literature, cognitive impairment was defined as having an adjusted Z score < -1.96 as compared with our control group mean performance. Comparisons of rates of impairments used Generalized Estimating Equations (GEE) methods for binary variables (logistic regression) which accounted for the repeated observations on individuals across time.

**Results**

A total of 303 patients enrolled in IHAST between February 1, 2002 and April 5, 2003 were screened at 21 participating centers. Two hundred and eighteen patients met eligibility criteria for CFAAST. All 218 eligible patients were approached for participation with 33 declining, leaving a study population of 185. Characteristics of the study population and those who declined to participate were well matched and are shown in Table 1.

Participant follow-up was excellent with 163 subjects (88.1%) and 163 (88.1%) of 185 returning for 9- and 15-month visits, respectively, and 152 (82.2%) completing all 3 assessments at 3, 9 and 15 months after initial craniotomy. Among the 45 control subjects, 42 (93.3%) were seen for second testing and 40 (88.8%) completed all 3 testing sessions at 6-month intervals. The median time intervals from craniotomy to neurological and cognitive testing for the 3-, 9- and 15-month assessments were 87, 281 and 463 days, respectively, with mean (±SD) values of 88 (±12), 279 (±17) and 464 (±20) days, respectively.

Table 2 shows comparative characteristics of patients assigned to normothermic and hypothermic groups, the control group, and entire CFAAST patient population. Characteristics of the 2 treatment groups (normothermia and hypothermia) were well matched in all respects. The control group was similarly comparable to the entire CFAAST population in terms of age, racial phenotype, gender and verbal IQ as assessed by the NART-R. The control group did have a slightly higher level of education (12.3±1.6 versus 11.6±2.7 years) and a lower depression score (5.8±6.6 versus 10.2±9.3), both of which achieved statistical significance.

Analyses of the composite scores (outcome variable) of the cognitive test battery by assessment time, treatment group and aneurysm location in CFAAST patients along with change in composite scores over time in the control group are shown in Table 3 and Figure, A. There was no significant effect for either treatment (hypothermia versus normothermia) or aneurysm location (anterior communicating artery versus all others). The impact of time was significant (\( P<0.001 \)) with improvement in composite scores with repeated testing over time seen in CFAAST patients as well as control subjects. This change in the control group performance, not unexpected, was attributed to the learning effect of repeated testing despite the use of alternate forms for administration of same tests.

Z scores (using adjustment method A) and change in Z scores (using method B) are presented in Table 4. A significant main effect for time was seen (\( P<0.001 \)). The means for both 9 months (−1.1±1.46) and 15 months (−1.1±1.38) were significantly different from the mean at 3 months (−1.4±1.48), with \( P<0.001 \) for both comparisons. The difference between 9- and 15-month scores was not significant (\( P=0.84 \)). There was no significant 2- or 3-way interactions. The composite Z scores were significantly related to NART-R score (\( P=0.02 \), but not to age (\( P=0.95 \)), aneurysm location (\( P=0.39 \)) or treatment group assignment (\( P=0.36 \)).

Z-score change over time (method B) is also shown in Table 4. Significant improvement in composite score performance (time effect) was noted from 3 months to both 9 and
15 months ($P<0.001$) with a plateau reached by 9 months such that the change between 9 and 15 months was not significant ($P=0.37$). Z scores for change in performance were significantly related to NART-R score ($P=0.013$), but not to age, aneurysm location, or treatment group (hypothermia or normothermia) assignment.

We defined cognitive impairment as a $Z$ score of $\leq -1.96$ based on the distribution of scores in the control group. Table 5 and Figure, B show the number of patients meeting this criterion of impairment in different groups at different times of testing. Overall, the number of patients with cognitive impairment was 35.7% at 3 months, 25.8% at 9 months, and 23.3% at 15 months. Frequency of cognitive impairment was not statistically related to treatment group assignment ($P=0.82$) or location of aneurysms ($P=0.33$), but had a significant relation to time such that the number of impaired patients at 9 and 15 months ($P<0.01$) was significantly less than those at 3 months. The rates of impaired patients at 9 and 15 months were not significantly different ($P=0.38$).

**Discussion**

This investigation is the first report of results of longitudinal assessment of cognitive function after SAH and aneurysm clipping with adjustment for the practice effects associated with repeated testing. Cognitive function, as measured by composite score, improved over time with significant improvement between 3 and 9 months and reached a plateau between 9 and 15 months after surgery. Although compromised cognitive function in patients with good neurological
outcome (as measured by the GOS) after SAH has been well documented in the literature, the majority of published studies are limited by their methodology, ie, the timing of follow-up has not been standardized and the effect of repeated testing on performance on cognitive function tests has not been accounted for. The time interval between SAH and cognitive evaluation has varied significantly between different studies as well as within the same study such that a clear time course of recovery could not be defined. Our data suggest that improvement in cognitive function continues beyond 3 months, which is the traditional duration of follow-up in most trials of neurological injury, including IHAST.

To date, no published study has examined the effect of intraoperative neuroprotection strategies used during aneurysm surgery on longitudinal postoperative cognitive function. The IHAST study provided information about the impact of mild intraoperative hypothermia on cognitive performance 3 months after surgery, and this investigation reports recovery beyond that time frame. Use of mild intraoperative hypothermia did not have a significant effect on

### TABLE 2. Characteristics of Patients With Hypothermia vs Normothermia and CFAAST Patients vs Control Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normothermia</th>
<th>Hypothermia</th>
<th>Normo- vs</th>
<th>CFAAST</th>
<th>Control Group</th>
<th>CFAAST vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Value</td>
<td>n</td>
<td>Value</td>
<td>P Value</td>
<td>PA</td>
</tr>
<tr>
<td>Age, years</td>
<td>96</td>
<td>52.3 ± 12.3</td>
<td>89</td>
<td>50.1 ± 13.0</td>
<td>0.28</td>
<td>51.3 ± 12.6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>31</td>
<td>32.3%</td>
<td>49</td>
<td>55.1%</td>
<td>0.08</td>
<td>71 (38.4%)</td>
</tr>
<tr>
<td>Females</td>
<td>65</td>
<td>67.7%</td>
<td>40</td>
<td>44.9%</td>
<td>0.11</td>
<td>114 (61.6%)</td>
</tr>
<tr>
<td>Racial Phenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North American</td>
<td>2</td>
<td>2.08%</td>
<td>0</td>
<td>0.00%</td>
<td>2 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Indian/Alaskan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
<td>0</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>1</td>
<td>1.04%</td>
<td>3</td>
<td>3.37%</td>
<td>4 (2.2%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Black or not of Hispanic origin</td>
<td>6</td>
<td>6.25%</td>
<td>5</td>
<td>5.62%</td>
<td>11 (5.9%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>1.04%</td>
<td>5</td>
<td>5.62%</td>
<td>6 (3.2%)</td>
<td>0</td>
</tr>
<tr>
<td>White, not of Hispanic origin</td>
<td>84</td>
<td>87.50%</td>
<td>71</td>
<td>79.78%</td>
<td>155 (83.8%)</td>
<td>40 (88.9%)</td>
</tr>
<tr>
<td>Indian/Pakistani</td>
<td>1</td>
<td>1.04%</td>
<td>0</td>
<td>0.00%</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>1</td>
<td>1.04%</td>
<td>5</td>
<td>5.62%</td>
<td>6 (3.3%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Education, years</td>
<td>96</td>
<td>11.9 ± 2.9</td>
<td>89</td>
<td>11.3 ± 2.5</td>
<td>0.20</td>
<td>11.6 ± 2.7</td>
</tr>
<tr>
<td>NART Scores</td>
<td>75</td>
<td>104.9 ± 13.2</td>
<td>67</td>
<td>100.8 ± 12.7</td>
<td>0.08</td>
<td>103 ± 13.1</td>
</tr>
<tr>
<td>Aneurysm Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>41</td>
<td>42.7%</td>
<td>31</td>
<td>34.8%</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Other location</td>
<td>55</td>
<td>57.3%</td>
<td>58</td>
<td>65.2%</td>
<td>18 (1.8%)</td>
<td>13 (17.1%)</td>
</tr>
<tr>
<td>Delayed ischemic neurological deficit (clinical evidence of vasospasm) present</td>
<td>18</td>
<td>18.8%</td>
<td>13</td>
<td>17.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd surgery within 2 weeks</td>
<td>4</td>
<td>4.2%</td>
<td>5</td>
<td>5.9%</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Depression (BDI score at 9-month visit)</td>
<td>87</td>
<td>10.0 ± 8.6</td>
<td>77</td>
<td>10.5 ± 10</td>
<td>0.9</td>
<td>10.2 ± 9.3</td>
</tr>
</tbody>
</table>

± values are mean ± SD.

### TABLE 3. Analysis of Composite Scores by Time, Treatment and Location in CFAAST Patients and Matched Control Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>3 Months (baseline)</th>
<th>9 Months</th>
<th>15 Months</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Score</td>
<td>n</td>
<td>Score</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>Normothermia</td>
<td>41</td>
<td>43.1 ± 9.8</td>
<td>38</td>
<td>45.1 ± 8.19</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>31</td>
<td>43.3 ± 7.5</td>
<td>27</td>
<td>48.1 ± 8.3</td>
</tr>
<tr>
<td>Other locations</td>
<td>Normothermia</td>
<td>55</td>
<td>43.0 ± 8.5</td>
<td>48</td>
<td>45.7 ± 9.5</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>58</td>
<td>41.4 ± 8.7</td>
<td>50</td>
<td>45.3 ± 8.9</td>
</tr>
<tr>
<td>Total CFAAST patients group</td>
<td>Both Groups combined</td>
<td>185</td>
<td>42.5 ± 8.7</td>
<td>163</td>
<td>45.8 ± 8.8</td>
</tr>
<tr>
<td>Control group*</td>
<td>Age, Sex and Education matched</td>
<td>45</td>
<td>50.7 ± 5.8</td>
<td>42</td>
<td>52.5 ± 6.0</td>
</tr>
</tbody>
</table>

Values are mean ± SD. NART-R score and age were included as covariates.

*Control group testing intervals are 0-months (baseline), baseline + 6 months and baseline + 12 months.
either composite scores or change in composite scores over
time up to 15 months postsurgery, nor did it affect the
frequency of patients with impaired cognitive function at
different time points. This result is consistent with the lack of
any treatment effect on neuropsychological outcomes in the
overall IHAST study group.5

Controversy exists regarding the impact of anatomical
location of the aneurysm on cognitive function after SAH.
Early studies21,25–27 suggested patients with anterior commu-
nicating artery aneurysms are particularly susceptible to
amnesia although recent reports23,24,27–31 failed to find a
difference related to aneurysm location. Lack of standardized
time of follow-up and small numbers of patients in some
investigations potentially contributed to the differences. In
one sizable study (n=114),31 patients were examined 7 to 115
months after craniotomy without any evident effects of lesion
location. The patients were examined at different stages of
recovery, and it is possible the effect of anatomical location
was masked by temporal recovery. In our patients, 39%
(n=71) of patients had anterior communicating artery aneu-
rysms. We compared composite scores of these patients to
those with aneurysms at all other sites and no significant
difference was identified.

Improvement in cognitive performance after surgery was
associated with the estimated premorbid verbal intellect as
assessed by the NART-R scores. The finding that higher
premorbid intellect was associated with greater recovery after
SAH and surgery agrees with the findings of Ogden et al31 and
TABLE 4. Composite Z Scores and Change in Z Scores in CFAAST Patients Adjusted for Learning Effect Seen in Control Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>3 Months</th>
<th>9 Months</th>
<th>15 Months</th>
<th>9–3 Months</th>
<th>15–3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Score</td>
<td>n</td>
<td>Score</td>
<td>n</td>
<td>Score</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>Normothermia</td>
<td>41</td>
<td>-1.3 (1.68)</td>
<td>38</td>
<td>-1.2 (1.36)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>31</td>
<td>-1.3 (1.28)</td>
<td>27</td>
<td>-0.7 (1.37)</td>
<td>29</td>
</tr>
<tr>
<td>Other locations</td>
<td>Normothermia</td>
<td>55</td>
<td>-1.3 (1.45)</td>
<td>48</td>
<td>-1.1 (1.57)</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>58</td>
<td>-1.6 (1.49)</td>
<td>50</td>
<td>-1.2 (1.48)</td>
<td>49</td>
</tr>
<tr>
<td>All patients</td>
<td>Both Groups</td>
<td>185</td>
<td>-1.4 (1.48)</td>
<td>163</td>
<td>-1.1 (1.46)</td>
<td>163</td>
</tr>
</tbody>
</table>

Two methods were used to adjust for learning effect (see text).

supports a more active model of brain reserve. Similar findings have been demonstrated in models of traumatic brain injury and electroconvulsive therapy. Higher intellect has also been associated with better health and longevity and less vulnerability to the impact of disease. Alternatively, it is possible that patients with high intellect lose the most intellect attributable to SAH and therefore have largest room for recovery.

CFAAST data reaffirm the importance of recruiting a matched control group, consistent with current recommendations, in longitudinal studies of postoperative cognitive function. The observed improvement in composite scores among controls can be attributed to practice effects. This occurred despite the use of alternate forms for repeated testing. This potential for nonrecovery associated improvement over time must be considered in longitudinal studies.

Limitations of the study include the possibility of sampling bias in the recruitment of a subset of patients from the IHAST study. For example, patients with poor cognitive outcome after surgery could potentially refuse participation at a disproportionate rate compared with those with good recovery. Our failure to identify any significant differences between recruited IHAST patients and those refusing participation on all measured variables influencing neuropsychiatric and cognitive test performance supports our belief that the CFAAST population is representative of overall IHAST patient population, though we cannot completely exclude the possibility of bias. Thirty three patients who refused to participate in CFAAST did have slightly lower composite score when examined 3 months after surgery (Table 1) although the difference did not reach a statistically significant level (P=0.6). Although there was no specific randomization of patients to normothermia or hypothermia groups for this trial, the permuted-block scheme used for randomization in IHAST, with stratification according to participating center and time between SAH and surgery, resulted in normothermia and hypothermia groups in CFAAST comparable not only demographically but also for preoperative (education, NART-R score and aneurysm location) and postoperative factors (delayed ischemic neurological deficit and second surgery in first 2 weeks and depression score at 9 months) likely to affect performance on cognitive testing.

There were also minor imbalances between the control group and CFAAST patients. The control group was matched for demographic variables to IHAST patients recruited before November 2002. Attributable to changes in the average education level of IHAST patients recruited into this study after November 2002, the education level in our final CFAAST group was slightly lower (11.6 versus 12.3 years) than the control group. Similarly, there was a slightly higher BDI score for depression (10.2 versus 5.8) in the CFAAST group. Although reaching statistical significance, this is of little clinical importance as both scores represent minimal depression (BDI score ≤13). An additional limitation is the control group’s recruitment from a single geographic area for comparison to a population obtained in an international study. A final limitation was the lack of premorbid baseline scores. This was unavoidable because patients seek care only after the onset of hemorrhage; therefore, we included the NART-R as a test of premorbid verbal IQ to assess cognitive function before SAH.

Summary
We conclude that improvement in cognitive function continues well beyond 3 months in patients with initial good
functional recovery after surgery for aneurysmal subarachnoid hemorrhage. Our data further suggest improvement reaches a plateau between 9 and 15 months postsurgery, and this has important implications in discussions with patients, families and healthcare providers while planning rehabilitation. The information is also useful for future clinical trials. Neither aneurysm location nor use of mild intraoperative hypothermia had a significant impact on cognitive function (using composite scores) or time course of recovery. We also suggest the use of NART-R, as a test of premorbid verbal IQ, may be helpful in predicting improvement in cognitive function.

Appendix

The members of CFAAST team were as follows:

University of Michigan–Steering Committee: S.K. Samra, MD; B. Giordani, PhD; A.F. Caveney, PhD; P.A. Scott, MD; and B.G. Thompson, MD.

Clinical Coordinating Center: S.K. Samra, A.F. Caveney, Bruno Giordani.


Data and Safety Monitoring Board: W. Young, Chair (University of California, San Francisco), R. Frankowski (University of Texas Health Science Center at Houston School of Public Health, Houston), K. Kieburtz (University of Rochester School of Medicine and Dentistry, Rochester, NY), D. Prough (University of Texas Medical Branch, Galveston), L. Sterman (Mt. Sinai Medical Center, Miami).


Participating Centers (the number of enrolled patients at each center is listed in parentheses) and members of the Neuropsychology teams are italicized:

Addenbrooke’s Hospital, Cambridge, United Kingdom (28): C. Salmon, D. Chaitfeld, B. Matta, P. Kirkpatrick.


Alfred Hospital, Melbourne, Australia (7): P. Bennett, P. Myles, J. Rosenfeld, J. Hunt, S. Wallace, H. Madder, W. Burnett, H. Fletcher.


Keck School of Medicine at University of Southern California, Los Angeles (7): C. McCleary, S. Giannotta, V. Zelman, E. Thomson, E. Babayyan, D. Fishback.


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University of Iowa Health Care, Iowa City (4): S. Anderson, K. Manzel, M. Maktabi, A. McAllister, J. Weeks.


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Disclosures

None.

References


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