Improvement and Impairment in Cognitive Function
After Carotid Endarterectomy: Comparison of Objective and Subjective Assessments

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Abstract

Objective and subjective assessments of postoperative improvement and impairment in cognition were prospectively compared in patients who underwent carotid endarterectomy (CEA). Each patient underwent subjective cognitive assessment by a neurosurgeon and the patient’s next of kin, and neuropsychological testing consisting of five test scores within 7 days before surgery and between 1 and 2 months after surgery. Of 213 patients studied, 24 (11%), 166 (78%), and 23 (11%) patients were defined as having subjectively improved, unchanged, and impaired cognition, respectively, following surgery. In all neuropsychological tests, differences in test scores between the two tests (postoperative test score – preoperative test score) significantly differentiated patients with subjectively improved, unchanged, and impaired cognition after surgery. Receiver operating characteristic analysis showed that the cut-off point for the differences in neuropsychological test scores in detecting subjective improvement and impairment in cognition after surgery was identical to mean + 2 standard deviations (SDs) and mean – 2 SDs, respectively, of the control value obtained from normal subjects. Of 27 patients with differences in neuropsychological test scores more than the upper cut-off point and 26 patients with differences in neuropsychological test scores less than the lower cut-off point in one or more neuropsychological tests, 24 (89%) and 23 (88%) exhibited subjectively improved and impaired cognition, respectively, after surgery. The present study indicates that neuropsychological test scores reflect the subjective assessment of postoperative change in cognition, and can detect subjective improvement and impairment in cognition after CEA using the optimal cut-off points for the test scores.

Key words: carotid endarterectomy, cognition, neuropsychological test

Introduction

Carotid endarterectomy (CEA) is an effective method for preventing stroke in appropriately selected patients. In addition, neurosurgeons and/or patients' families often report postoperative subjective improvements or impairments in cognition for patients undergoing CEA. In fact, numerous studies have investigated objective changes in cognitive function following CEA using neuropsychological testing: just over half of these studies reported an improvement in cognition after CEA, but the remainder found no change.1,10,15,16,20,25,28 Recent studies have demonstrated that cognitive impairment occurs in 10% to 30% of patients following CEA.7,8,14,21 Such variation in results may depend on differences in methodological factors, including sample size, type of patient and control group, severity and side of carotid artery stenosis, range of neuropsychological testing, and the timing of postoperative assessment. No clear guidelines have been established for determining significant objective improvements or impairments in performance because such changes may, in part, reflect the “practice effect” (an improvement in scores when patients are repeatedly tested).13,20 Further, the relationship between subjective and objective assessments remains unknown.

The present study prospectively compared objective and subjective assessments of improvement or impairment in cognition after CEA, to suggest guidelines for determining significant improvement or impairment in cognition.
Patients and Methods

A total of 296 patients who underwent CEA from April 2000 to December 2007, of whom 237 patients satisfied the protocol criteria and were prospectively entered into the present study. The criteria were as follows: age, ≤75 years; ipsilateral severe internal carotid artery (ICA) stenosis (≥70%) on angiography with arterial catheterization; preoperative useful residual function (modified Rankin disability scale 0 or 1); no ipsilateral carotid artery territory ischemic symptoms within the last 6 months or ipsilateral carotid artery territory ischemic symptoms that had occurred >2 weeks before presentation to our department; no further ischemic symptoms during the period between initial evaluation and surgical intervention; no new major neurological deficits on recovery from anesthesia following surgery for CEA; and written informed consent obtained from both the patient and next of kin. This study was reviewed and approved by the institutional ethics committee of Iwate Medical University.

The same surgeon (K.O.) performed CEA for all patients who were entered into the present study, under general anesthesia with the use of an operating microscope from the skin incision. Neither intraluminal shunt nor patch grafts were used in these procedures. A bolus of heparin (5000 U) was given prior to ICA clamping.

Cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to acetazolamide was preoperatively assessed using iodine-123 N-isopropyl-p-iodoamphetamine and single photon emission computed tomography (SPECT) as described previously.22 CBF was also measured immediately after surgery at the same fashion. Based on the CBF values measured using the brain perfusion SPECT, post-CEA hyperperfusion was defined as described previously.22 Diffusion-weighted magnetic resonance (MR) imaging was performed before and within 24 hours after surgery to identify development of new postoperative ischemic lesions.

Patients visited the neurosurgeon (K.O.) in our outpatient clinic within 7 days before surgery and between 1 and 2 months after surgery. At the postoperative visit, the neurosurgeon subjectively assessed whether cognition was improved, impaired, or unchanged after surgery compared with the preoperative cognition. A neurologist unaware the neurosurgeon’s assessment also asked the next of kin whether the patient’s cognition was improved, impaired, or unchanged after the surgery compared with the preoperative cognition. Subjective improvement or impairment in cognition after surgery was defined as when both the neurosurgeon and the next of kin agreed on postoperative improvements or impairments in cognition. Subjectively unchanged cognition after surgery was defined as other combinations of assessments of the neurosurgeon and the next of kin.

Objective assessment of postoperative changes in cognition was based on a battery of neuropsychological tests, consisting of the Japanese translation of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),27 the Japanese translation of the Wechsler Memory Scale (WMS),17 and the Rey-Osterreith Complex Figure test (Rey test).18 The WAIS-R provides measures of general intellectual function and generates a verbal and performance intelligence quotient (IQ). The WMS assesses orientation, recall of current information, recall of passages, sustained attention, digit span, and new learning of associative word pairs. The Rey test evaluates copy and recall of a complex figure, to assess visuospatial constructional ability and visual memory. The subtests within the Rey test include the copy trial, in which the subject copies a drawing of a complex figure, and a recall trial, in which the subject draws the figure from memory after a 30- to 45-minute delay. Thus, 5 scores (WAIS-R verbal IQ, WAIS-R performance IQ, WMS, Rey copy, and Rey recall) were used to objectively evaluate cognitive function.

The preoperative and postoperative neuropsychological tests were performed within 7 days after the subjective assessment of cognition, and differences in each neuropsychological test score between the two tests (postoperative test score − preoperative test score) were calculated and defined as the Δ score. All examinations were administered by a trained neuropsychologist who was unaware of the clinical information.

Forty healthy volunteers (37 men and 3 women; mean age 60 years, range 45–70 years) served as controls and underwent the same neuropsychological tests on two separate occasions. None of these healthy volunteers had a past history of hypertension, diabetes mellitus, atrial fibrillation, pulmonary disease, leukoaraiosis, or asymptomatic lacunar infarction on conventional brain MR imaging. The interval between the two tests ranged from 1 to 2 months. Differences in each neuropsychological test score between the two tests (second test score − first test score), defined as the Δ score in controls, were 3.4 ± 4.5 (mean ± standard deviation [SD]) on the WAIS-R verbal IQ, 4.9 ± 5.0 on the WAIS-R performance IQ, 4.7 ± 6.1 on the WMS, 0.4 ± 1.1 in the Rey copy, and 2.9 ± 3.5 on the Rey recall.

To evaluate the inter-observer (neurosurgeon and next of kin) agreement of the subjective assessment of postoperative changes in cognition of patients,
the proportion of concordant assessments was calculated as the number of concordant assessments divided by the number of assessments by the neurosurgeon and/or the next of kin. Data are expressed as the mean ± SD. Differences or incidences of patient characteristics between three groups were evaluated using the \( \chi^2 \) test followed by Bonferroni’s inequality correction or Scheffe’s F test. Changes between pre- and postoperative neuropsychological scores were evaluated using the Wilcoxon signed-rank test. Differences of \( \Delta \) score in each neuropsychological test between the three groups were examined using Scheffe’s F test. Differences were deemed significant for values of \( p < 0.05 \). The accuracy of \( \Delta \) score in each neuropsychological test in detecting subjective improvement and impairment in cognition after surgery was assessed using receiver operating characteristic (ROC) curves. The ROC curve was calculated in increments and decrements of 0.5 SD from the mean value of \( \Delta \) score obtained in normal subjects.

**Results**

Of 237 patients who satisfied the inclusion criteria, 24 did not undergo postoperative neuropsychological testing and were excluded from the analysis. Thus, 213 patients were analyzed into the present study, 198 men and 15 women aged 45 to 75 years (mean ± SD 68.1 ± 5.8 years), of whom 157 patients had hypertension, 71 had diabetes mellitus, and 50 had hyperlipidemia; 146 patients exhibited modified Rankin scale of 0 and 67 showed 1; 138 patients had ipsilateral carotid artery territory symptoms and the remaining 75 patients had asymptomatic ICA stenosis. Preoperative MR imaging showed infarction in the cerebral hemisphere ipsilateral to surgery in 105 patients. The duration of ICA clamping ranged from 19 to 55 minutes (mean 35.1 minutes).

Table 1 shows the inter-observer agreement for the subjective assessment of postoperative change in cognition. The concordance rates for the subgroups of patients who were assessed were 0.80 (24/30) postoperatively improved, 0.94 (156/166) unchanged, and 0.85 (23/27) impaired cognition. Thus, 24 (11%), 166 (78%) and 23 (11%) patients had subjectively improved, unchanged, and impaired cognition, respectively, after surgery.

Table 2 compares patient characteristics between these three groups. Preoperative CBF was significantly lower in patients with subjectively improved cognition after surgery than in those with

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**Table 1** Inter-observer agreement of subjective assessment of postoperative change in cognition

<table>
<thead>
<tr>
<th>Assessment by neurosurgeon</th>
<th>Assessment by next of kin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative change in cognition</td>
<td>Number of patients</td>
</tr>
<tr>
<td>Improved</td>
<td>28</td>
</tr>
<tr>
<td>Unchanged</td>
<td>162</td>
</tr>
<tr>
<td>Impaired</td>
<td>23</td>
</tr>
</tbody>
</table>

**Table 2** Comparison of patient characteristics in the three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>A: Improved (n = 24)</th>
<th>B: Unchanged (n = 166)</th>
<th>C: Impaired (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>67.3 ± 5.2</td>
<td>68.1 ± 4.6</td>
<td>66.7 ± 7.8</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>79% (19/24)</td>
<td>89% (147/166)</td>
<td>87% (20/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63% (15/24)</td>
<td>74% (122/166)</td>
<td>87% (20/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38% (9/24)</td>
<td>33% (54/166)</td>
<td>35% (8/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>21% (5/24)</td>
<td>23% (39/166)</td>
<td>26% (6/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Modified Rankin scale of 0</td>
<td>63% (15/24)</td>
<td>69% (114/166)</td>
<td>74% (17/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>71% (17/24)</td>
<td>63% (105/166)</td>
<td>70% (16/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Infarction on MR imaging</td>
<td>63% (15/24)</td>
<td>48% (80/166)</td>
<td>43% (10/23)</td>
<td>NS</td>
</tr>
<tr>
<td>CBF (ml/100 g/min)*</td>
<td>27.6 ± 2.4</td>
<td>32.6 ± 6.5</td>
<td>30.2 ± 4.6</td>
<td>0.0009</td>
</tr>
<tr>
<td>CVR (%)*</td>
<td>17.2 ± 9.3</td>
<td>34.4 ± 17.6</td>
<td>16.8 ± 19.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of ICA clamping (min)*</td>
<td>34.9 ± 5.7</td>
<td>35.6 ± 6.4</td>
<td>34.7 ± 6.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± standard deviation. CBF: cerebral blood flow, CVR: cerebrovascular reactivity, ICA: internal carotid artery, MR: magnetic resonance, NS: not significant.
subjectively unchanged cognition. Preoperative CVR was significantly lower in patients with subjectively improved or impaired cognition after surgery than in those with subjectively unchanged cognition. Of the 23 patients with subjectively impaired cognition after surgery, 14 developed postoperative cerebral hyperperfusion on brain perfusion SPECT imaging and 3 had new postoperative spotty ischemic lesions on diffusion-weighted MR imaging, whereas one patient exhibited both conditions.

Results from the five neuropsychological tests conducted before and after CEA are summarized in Table 3. All test scores were significantly increased after surgery. Figure 1 shows the relationship between the subjective assessment of postoperative change in cognition and Δ score in each neuropsychological test. The Δ score significantly differentiated patients with subjectively improved, unchanged, and impaired cognition after surgery in all neuropsychological tests.

Sensitivity, specificity, and positive and negative predictive values for the Δ score in each neuropsychological test using the cut-off point lying closest to the left upper corner of the ROC curve for detecting subjective improvement and impairment in cognition after surgery are summarized in Table 4. In all neuropsychological tests, the cut-off point of the Δ score was identical to the mean +2 SDs and the mean −2 SDs, respectively, of the control value obtained from normal subjects. Further, of the 27 patients with Δ score more than the mean +2 SDs of the control value in one or more neuropsychological tests, 24 and 3 exhibited subjectively improved and unchanged cognition, respectively, after surgery. Of the 26 patients with Δ score less than the mean −2 SDs of the control value in one or more neuropsychological tests, 23 and 3 (exhibited subjectively impaired and unchanged cognition, respectively, after surgery.

Table 3 Neuropsychological test scores before and after surgery

<table>
<thead>
<tr>
<th>Test</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R verbal IQ</td>
<td>87.4±13.3</td>
<td>91.2±14.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WAIS-R performance IQ</td>
<td>88.2±13.8</td>
<td>92.7±15.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WMS</td>
<td>95.6±19.0</td>
<td>99.2±20.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rey copy</td>
<td>32.3±4.3</td>
<td>33.0±4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rey recall</td>
<td>21.7±6.8</td>
<td>24.0±7.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. IQ: intelligence quotient, Rey copy: Rey-Osterreith Complex Figure test copy trial, Rey recall: Rey-Osterreith Complex Figure test recall trial, WAIS-R: Wechsler Adult Intelligence Scale-Revised, WMS: Wechsler Memory Scale.

Fig. 1 Box plot representing the relationship between subjective assessment of postoperative change in cognition and Δ score in each neuropsychological test. A: Wechsler Adult Intelligence Scale-Revised (WAIS-R) verbal intelligence quotient (IQ), B: WAIS-R performance IQ, C: Wechsler Memory Scale, D: Rey-Osterreith Complex Figure test copy trial, E: Rey-Osterreith Complex Figure test recall trial. *p < 0.0001.
All 160 patients with $\Delta$ score between the mean $+2$ SDs and the mean $-2$ SDs of the control value in all neuropsychological tests exhibited subjectively unchanged cognition after surgery.

**Discussion**

A recent study has suggested that normalization of cerebral metabolism via improvements in cerebral hemodynamics after CEA may result in cognitive improvement as well as functional recovery of the neurotransmitter system. Further, preoperative low CBF in the cerebral hemisphere ipsilateral to surgery is significantly associated with postoperative cognitive improvement. Our present findings correspond to this previous observation.

Investigators have hypothesized that cognitive impairment after CEA may result from three possible mechanisms: First, to perform CEA, the ICA and common carotid arteries are cross-clamped, causing a transient decrease in CBF in the ipsilateral middle cerebral artery territory in many patients. If the reduction in hemispheric perfusion is significant enough to impair neuronal functioning, postoperative impairment of cognitive function may result. Further, development of postoperative cognitive impairment may be theoretically dependent on the intensity and duration of cerebral ischemia during ICA clamping. However, intraoperative cerebral oxygen saturation monitoring with near-infrared spectroscopy has demonstrated that the degree of cerebral ischemia during ICA clamping was significantly more intense in patients with postoperative cognitive impairment than in those without, so duration of ICA clamping was not associated with the development of postoperative cognitive impairment. The present study includes no findings regarding intensity of cerebral ischemia during ICA clamping, but the relationship between duration of ICA clamping and postoperative cognitive change corresponded with previous findings.

Second, many patients exhibit evidence of gaseous and particulate emboli in the middle cerebral artery during CEA. Particulate embolization during surgery correlates with neuropsychological deterioration. Third, cerebral hyperperfusion syndrome is a complication after CEA and is characterized by unilateral headache, face and eye pain, seizure, and focal symptoms that occur secondary to cerebral edema or intracerebral hemorrhage. Post-CEA hyperperfusion, even when asymptomatic, causes postoperative cortical neural damage that results in postoperative cognitive impairment. In the present study, based on findings of pre- and postoperative neuroimaging, 65% and 17% of patients with subjectively impaired cognition after surgery developed cerebral hyperperfusion and cerebral embolization from the surgical site, respectively; and the remaining patients may have had subjectively impaired cognition after surgery due to hemispheric hyperperfusion during ICA clamping.

All previous studies regarding cognitive change after CEA used neuropsychological testing to define postoperative cognitive improvement or impairment. Neuropsychological tests are regarded as objective measures of cognition, but the criterion for defining significant postoperative improvement or impairment in neuropsychological tests remains undetermined. Neurosurgeons and/or patients’ families often report postoperative subjective improvements or impairments in cognition for patients undergoing CEA, so we defined subjective assessments.
based on personal judgments as significant postoperative changes in cognition. However, subjective determinations of cognitive change may not always correspond between the neurosurgeon and the next of kin. However, the concordance rates for each subgroup of patients assessed as postoperatively improved, impaired, or unchanged cognition by the neurosurgeon and the next of kin was 0.80 or more, representing good agreement. Finally, patients who underwent CEA were defined as having subjectively improved cognition in 11% and impaired cognition in 11% after surgery.

In the 213 patients studied, neuropsychological test scores were significantly increased after surgery compared with the preoperative values, corresponding to previous studies.\(^2,21,23,26\) These phenomena reportedly develop even in patients who underwent uncomplicated neck clipping through craniotomy for unruptured cerebral aneurysms.\(^23\) These group-rate analyses are strongly influenced by the practice effect,\(^21,23\) so whether cognition is improved or not after surgery should not be determined using only results of such group-rate analyses. In contrast, in a recent substudy of the International Carotid Stenting Study (ICSS),\(^2\) raw neuropsychological scores per individual at baseline and follow up were expressed as SD units: the so-called z scores. These z scores were calculated using data of healthy volunteers, so controlling for potential practice effects in patients. The group-rate analyses in the ICSS found no significant changes in the neuropsychological z scores after CEA.

Prior to this ICSS report, the relationship between subjective assessment such as the feelings of neurosurgeons or patients’ families and objective assessment such as neuropsychological testing had not been reported. The present study demonstrated that the degree of postoperative increase or decrease in neuropsychological test scores differentiated patients with subjectively improved, unchanged, and impaired cognition after surgery, and that the cut-off point of the degree of postoperative increase or decrease in neuropsychological test scores in detecting subjective improvement and impairment in cognition after surgery was identical to the mean +2 SDs and the mean -2 SDs, respectively, of the control value obtained from normal subjects. Furthermore, approximately 90% of patients with postoperative increase in test scores more than the upper cut-off point and postoperative decrease in test score less than the lower cut-off point in one or more neuropsychological tests exhibited subjectively improved and impaired cognition, respectively, after surgery. All patients with postoperative increases or decreases in test scores between the upper and lower cut-off points in all neuropsychological tests exhibited subjectively unchanged cognition after surgery. These findings suggest that neuropsychological test scores reflect the subjective assessment of postoperative change in cognition and detect subjective improvement and impairment in cognition after surgery when the optimal cut-off points for the test score are defined.

The present study possesses a serious limitation that requires discussion. We cannot estimate the extent of observer bias associated with the subjective assessments of a patient’s condition. However, we determined that the inter-observer agreement between the neurosurgeon and the next of kin was good, though the reliability and reproducibility of these assessments remain unknown.

The present study suggests that neuropsychological test scores reflect subjective assessments of postoperative change in cognition and can detect objective improvement and impairment in cognition after surgery. Significant postoperative improvement or impairment in cognition using neuropsychological testing is based on the optimal cut-off points for the test scores, mean +2 SDs or mean -2 SDs of the control value.

References


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