From the Western Vascular Society

Incidence, outcomes, and effect on quality of life of cranial nerve injury in the Carotid Revascularization Endarterectomy versus Stenting Trial

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Objective: **Cranial nerve injury (CNI) is the most common neurologic complication of carotid endarterectomy (CEA) and can cause significant chronic disability. Data from prior randomized trials are limited and provide no health-related quality of life (HRQOL) outcomes specific to CNI. Incidence of CNIs and their outcomes for patients in the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) were examined to identify factors predictive of CNI and their impact on HRQOL.**

Methods: **Incidence of CNIs, baseline and procedural characteristics, outcomes, and HRQOL scores were evaluated in the 1151 patients randomized to CEA and undergoing surgery ≤30 days. Patients with CNI were identified and classified using case report forms, adverse event data, and clinical notes. Baseline and procedural characteristics were compared using descriptive statistics. Clinical outcomes at 1 and 12 months were analyzed. All data were adjudicated by two neurologists and a vascular surgeon. HRQOL was evaluated using the Medical Outcomes Short-Form 36 (SF-36) Health Survey to assess general health and Likert scales for disease-specific outcomes at 2 weeks, 4 weeks, and 12 months after CEA. The effect of CNI on SF-36 subscales was evaluated using random effects growth curve models, and Likert scale data were compared by ordinal logistic regression.**

Results: **CNI was identified in 53 patients (4.6%). Cranial nerves injured were VII (30.2%), XII (24.5%), and IX/X (41.5%), and 3.8% had Horner syndrome. CNI occurred in 52 of 1040 patients (5.0%) receiving general anesthesia and in one of 111 patients (0.9%) operated on under local anesthesia ($P = .05$). No other predictive baseline or procedural factors were identified. Deficits resolved in 18 patients (34%) at 1 month and in 42 of 52 patients (80.8%) by 1 year. One patient died before the 1-year follow-up visit. The HRQOL evaluation showed no statistical difference between groups with and without CNI at any interval. By Likert scale analysis, the group with CNI showed a significant difference in the difficulty eating/swallowing parameter at 2 and 4 weeks ($P < .001$) but not at 1 year.**

Conclusions: **In CREST, CNI occurred in 4.6% of patients undergoing CEA, with 34% resolution at 30 days and 80.8% at 1 year. The incidence of CNI was significantly higher in patients undergoing general anesthesia. CNI had a small and transient effect on HRQOL, negatively affecting only difficulty eating/swallowing at 2 and 4 weeks but not at 1 year. On the basis of these findings, we conclude that CNI is not a trivial consequence of CEA but rarely results in significant long-term disability. (J Vasc Surg 2015;61:1208-15.)**

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Injury to cranial nerves (CNs) is the most common neurologic complication of carotid endarterectomy (CEA) and, when unresolved, may result in significant long-term disability. These injuries have been a well-known complication of the procedure since its inception and have been the topic of numerous publications.[1-9] Generally, most of the injuries resolve, and although there is potential for significant long-term disability, it is relatively rare.

Multiple surgical series have reported the incidence of CN injury (CNI), but rates are highly variable, ranging from 3% to 30%.[1-9] This variability is one of measurement error, largely a consequence of the intensity of evaluation and diagnostic modalities used. In clinical trials that included a CEA arm, CNI has been reported as occurring in 5.1% to 8.6 % of cases.[10-13] In studies where patients underwent a detailed otolaryngologic examination preoperatively and postoperatively to evaluate CN function, injury was found to occur after 11.5% to 39% of operations.[2,3,9,14,15] In contrast, two recent large series

using the usual clinical criteria alone found an incidence of 5.5% and 5.6%.[16,17] Most of these injuries resolve within a few weeks, but the neurologic deficit can be shown to be persistent in as high as 7% to 12% of patients, depending on the depth of scrutiny.[14,17]

The CNs can be injured during CEA by the surgical dissection, traction, electrocautery, clamp injury, or compression by a postoperative hematoma. The most commonly injured nerves are the recurrent or superior laryngeal branches of the vagus nerve (CN X), the hypoglossal nerve (CN XII), the marginal mandibular branch of the facial nerve (CN VII), and the glossopharyngeal nerve (CN IX). Depending on the nerve that is injured, deficits vary from a minor nuisance to a severe disability that may require a feeding tube or tracheostomy, or both.

The availability of carotid artery stenting (CAS) as an alternative therapy to CEA for carotid artery stenosis has generated renewed interest in the topic of CNI because the former procedure does not put patients at risk for this complication. Some proponents of CAS have argued that the morbidity of CNI may be equivalent to that of a minor stroke and mitigates some of the benefit of the reduction in neurologic complications seen in the CEA arm in most clinical trials comparing the two procedures.[13]

The Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) compared CEA with CAS in 2502 symptomatic and asymptomatic patients randomly assigned to undergo one of the two procedures. The primary results of the trial showed no difference in the composite end point of stroke, myocardial infarction, and death between the two therapeutic options.[18] The individual end points of periprocedural myocardial infarction and stroke were more common in the CEA and CAS arms of the study, respectively. In addition to the primary end point evaluations, patients in CREST underwent a health-related quality of life (HRQOL) assessment as part of the trial. The purpose of the study reported here was to carefully examine the incidence, potential predictive factors, and HRQOL outcomes in the patients experiencing CNI in CREST.

METHODS

CREST is a prospective, randomized, multicenter trial with blinded end point adjudication that compared the safety of CEA vs CAS in patients with either symptomatic or asymptomatic high-grade extracranial carotid stenosis. Details of the trial design have been previously reported.[18,19] Participants were enrolled from December 2000 through July 2008 at 117 clinical centers in the United States and Canada. The protocol was approved by the institutional review boards/ethics committees at participating sites, and all participants provided signed informed consent.

Assessment of CNI at 1 and 6 months postprocedure was a preplanned secondary analysis, and these results have been previously reported.[18] Although some studies have included injury to cervical sensory nerves in their reports, we decided to not include those injuries in this report because they are common, do not cause significant disability, and are largely unavoidable. For this analysis, the assessment of CNI outcomes was extended to 12 months postprocedure. The study cohort included the 1151 patients who were assigned to the CEA arm of the study and were treated with CEA ≤30 days of randomization. Five additional patients with CNI were excluded from this analysis because they did not receive CEA within the 30-day window or were crossovers from the CAS arm of the study. Their outcomes are described below.

Patients with CNI were identified and classified using case report forms, adverse event data, and clinical notes. Injuries were classified as resolved if stated as such in case report forms or clinical notes or if a deficit was no longer noted in clinical notes or on the National Institutes of Health Stroke Scale evaluations. Sites were contacted regarding individual cases if the available data were unclear. Criteria used for diagnosis of CNI are contained in Table I. Adjudication of the CNIs was performed by two neurologists and a vascular surgeon. For the purpose of this study, injuries to the vagus and glossopharyngeal nerves were grouped because the available data did not always allow a precise differentiation of which nerve had been injured.

HRQOL was evaluated using a standardized self-administered questionnaire at baseline (before the procedure) and at 1 and 12 months postprocedure, and by a telephone interview 2 weeks after the procedure. The Medical Outcomes Study Short-Form 36 (SF-36) Health Survey measures eight dimensions of health (physical functioning, physical role limitations, bodily pain index, vitality, general health, social functioning, emotional role limitations, and mental health) and has been validated in patients with cardiovascular disease and stroke.[20-22] Six disease-specific Likert scales designed specifically for comparison of CAS vs CEA were used to evaluate aspects of functional status and symptoms that may be affected by one or both of the treatments. The Likert scales included in this analysis were difficulty eating/swallowing, headaches, neck pain, difficulty walking, difficulty driving, and leg pain. These two measures of HRQOL (the SF-36 and Likert scales) were used to compare outcomes between patients who underwent CEA and were diagnosed with CNI vs those who did not have CNI.

Statistical analysis. Baseline demographic characteristics and operative procedural characteristics were compared between the groups with and without CNI using χ^2 for categorical variables and *t*-tests for continuous variables.

Random effects growth curve models were used to examine the effect of periprocedural CNI on each of the SF-36 subscales over time (relative to no CNI). These models readily accommodate HRQOL score changes (linear or nonlinear) over time as well as missing data patterns commonly seen in longitudinal studies. Under the assumption of missing at random, subjects with missing data at one or more time points can be retained in the analysis, such that this approach can use all available data collected in the study. The outcome