LEADING ARTICLE

# Cranial Nerve Palsy Should Not Be Included within a Primary Composite Endpoint in Carotid Surgery Trials

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Carotid endarterectomy (CEA) is the most commonly performed surgical procedure for the treatment of extracranial cerebrovascular atherosclerosis and the risk of major peri-operative neurologic complications has been thoroughly documented. By contrast, the incidence and significance of iatrogenic injury to cranial nerves during the procedure has not been so rigorously scrutinized. Cranial nerve palsy (CNP) is a recognized complication of CEA and its reported frequency (3—23%) varies according to study design, method of diagnosing the injury and whether or not the patient was assessed independently by a Neurologist.

The largest available series where patients were studied before and after surgery was the European Carotid Surgery Trial (ECST). They observed 88 motor cranial nerve injuries among 1739 patients giving an early CNP rate of 5.1% (95% CI 4.1—6.2), falling to 0.5% (95% CI 0.24—0.98) at 4 months, none of which subsequently resolved.[1] Asymptomatic CNP was not documented by the ECST and this probably contributed to the relatively low risk of CNP compared with other prospective studies which utilized more sophisticated testing modalities (e.g. otolaryngoscopy). The 5.1% risk of postoperative CNP in ECST is also lower than the 8.6% risk reported in the North American Symptomatic Carotid Endarterectomy (NASCET) trial.[2] In ECST, the initial clinical assessment was made by the operating surgeon and the patient was not examined by a neurologist until a few months following surgery. For these reasons it is likely that the ECST data under-estimate the immediate postoperative risk. Nevertheless, ECST does provide reliable data on the prevalence of persisting symptomatic deficits during longer-term follow-up, observing that the rate of permanent CNP was very low (0.5%).

To minimize the risks of CNP, carotid angioplasty with stenting (CAS) was developed as an alternative to CEA. In the International Carotid Stenting Study (ICSS),[3] 45 CNPs (5.5%) were observed in 821 patients allocated to surgery, of which only one (0.1%) was judged to be disabling at one month.[3,4] Only two CEA patients suffered CNPs which did not resolve in the long-term and the median duration of symptoms before the CNP resolved was 30 days (2—520 days). In the Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE-1) trial, a transient CNP in the early postoperative period was documented in 17 (8.2%) patients after eversion CEA and in 25 (8.1%) patients after conventional CEA.[5] When all the European randomized CAS vs CEA trial data were combined, the mean CNP rate after CEA was 6.0%, suggesting that while the rates of peri-operative stroke or death after CEA may have reduced over the last two decades, the same cannot be said of CNP.[6]

In the North-American Carotid Revascularization Endarterectomy versus stenting Trial (CREST), neurologic evaluations were conducted prior to treatment and then at 24—48 hours post-intervention, one month, three months and then annually.[7] CNP was observed in 0.3% of CAS patients and 4.7% of CEA patients, although another paper from CREST reported a 5.0% CNP rate after CEA.[8] In the early post intervention period, CAS patients reported less difficulty in eating and swallowing compared with CEA patients. However, by 12 months CNP was not associated with a sustained impact on HRQOL (Health related quality of life).[7]

Recently, Fokkema et al. presented CNP data from the Vascular Study Group of New England (VSGNE) in 6,878 patients undergoing CEA between 2003 and 2011.[9] The surgeon-observed CNP rate was determined at the time of discharge and again at a median of 12 months. The prevalence of early CNP was 5.6% (382 patients) and most were transient. Only 47 patients (0.7%) had a persisting CNP at 12 months. These data are, therefore, very similar to what was observed in the randomized trials with independent Neurologist scrutiny.

VSGNE also observed that a prior history of ipsilateral CEA or cervical irradiation (often considered to confer an increased risk of CNP) were not actually associated with a significant increase in CNP.[9] These observations are consistent with a recent meta-analysis of CNP in CEA patients with a prior history of cervical irradiation (12 studies, 157 patients) which observed a prevalence of 9.2% (95% CI 3.7%—21.1%).[10] In this meta-analysis, most of the CNPs were transient and had completely resolved within several weeks. Six studies reporting on this specific endpoint did not report any CNP problems at all. These data suggest that a history of prior cervical irradiation should not be considered to be an absolute contra-indication to performing CEA.

Although most surgeons consider CNPs to be relatively minor (compared with central neurological morbidity), multiple or bilateral CNPs can be quite disabling, particularly if the swallowing mechanism or laryngeal airway are affected. The overall prevalence of CNP is similar to the

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composite endpoint of death, stroke and myocardial infarction after CEA and some believe that CNP should be included within any composite outcome analysis. However, the 5% prevalence of CNP (mostly transient) should not deflect attention away from the most critical priority of preventing stroke and stroke related death. To date, there is no evidence that by excluding CNP from the composite primary endpoint in the randomized trials of CAS vs CEA, that any of the conclusions would have been altered. Randomized controlled trials (RCT) are designed to see if the intervention does or does not provide a better outcome than the gold standard treatment of the time. In some of the more recent randomized trials comparing CAS with CEA, the primary endpoint has included death, stroke, and myocardial infarction within 30 days. Many consider that the inclusion of myocardial infarction within the primary endpoint was probably an error[11] and this would be further compounded by the inclusion of CNP, because this would imply that a subclinical CNP was equally as important as death. In short, the efficacy of CEA should not be confused with safety. CEA is performed to reduce the incidence of death & stroke and it does this, but at a short term cost of procedural complications that should be counted on the safety side. CNP is a recognized complication of CEA just like a femoral haematoma is a complication of CAS. Both should be recorded, but neither should be considered primary endpoints.

In conclusion; the risk of CNP after CEA persisting beyond hospital discharge is approximately 6%. The vast majority will resolve over the first few months and permanent deficits are rare (<1%). A very small proportion of CNPs will, however, be disabling and patients should be given clear and accurate information regarding the likelihood of sustaining such an injury before undergoing surgery. Finally; the very low risk of suffering a permanent or disabling CNP should not detract from the significant benefit conferred by CEA (regarding stroke prevention), especially in the early time period after onset of symptoms.

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