

STROKE

Optimization of the timing of carotid endarterectomy

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Carotid endarterectomy reduces the risk of stroke in patients with symptomatic carotid artery stenosis, but the optimum time to perform surgery has been uncertain. A large study has shown that surgery within 2 days of stroke or transient ischaemic attack has an unacceptable complication rate, but is safe thereafter.

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Carotid artery endarterectomy (CEA) aims to remove atherosclerotic plaque from the carotid artery, preventing thrombus formation on the plaque, which could otherwise lead to a stroke or transient ischaemic attack (TIA). This approach does, however, entail a risk of perioperative stroke. The timing of CEA after ischaemic symptoms has been a topic of considerable interest for many years. A large study in Sweden¹ has now shed light on this issue, with findings that suggest an update to current guidelines are warranted.

After the publication of results from the North American Symptomatic Carotid Endarterectomy Trial (NASCET)² and the European Carotid Surgery Trial (ECST),³ guidelines for stroke care in the USA, Europe and elsewhere recommended operating on patients with symptomatic carotid stenosis within 6 months of the presenting ischaemic event. In 2004, a pooled analysis of data from NASCET and ECST was conducted to determine the effect of surgery, including surgery timing, on outcome in various subgroups.⁴ The study concluded that patients benefited most from an operation within 2 weeks of an ischaemic event, and thereafter, this benefit decreased with time from event to surgery.⁴ As a consequence of the above findings, clinical guidelines were revised. In 2004, the UK National Clinical Guidelines for Stroke stated that CEA should be performed within 2 weeks of recent stroke or TIA.⁵ These guidelines have subsequently been echoed by the American Heart and Stroke Associations,⁶ and by the European Stroke Organisation,⁷ and have been widely implemented in clinical practice.

Many surgeons have interpreted the guidelines as indicating that CEA should be performed as soon as possible after symptoms appear, and some guidelines encouraged carotid intervention within 48 h of an ischaemic event. This recommendation, however, was not evidence-based as too

few ischaemic events occurred in carotid surgery trials to analyse the balance of risk and benefit in patients treated within 48 h. Concern remained that very early surgery might be harmful.

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Several studies have been carried out, both retrospectively and prospectively, to establish whether the benefit of immediate carotid surgery in preventing recurrent stroke outweighs the risk of procedure-associated stroke and death. Several studies, published between 2002 and 2011, reported no significant difference in the safety of CEA carried out in the early or hyperacute period after an ischaemic event compared with surgery at a later time point. For example, in a cohort of 104 patients with ischaemic stroke, Rantner *et al.* reported no perioperative complications in seven patients who underwent CEA within 24 h of stroke.⁸ Overall, however, 3.4% of patients who underwent surgery within 4 weeks of stroke experienced complications, but this proportion is comparable to the 4.8% of patients who experienced complications when treated after 4 weeks. 12% of patients awaiting an operation had a recurrent ischaemic event or an arterial occlusion, most of which occurred in the third or fourth week after initial stroke or TIA.⁸ Similarly, Salem *et al.* found no significant difference between perioperative complications in patients who underwent surgery within 14 days of an ischaemic event versus those who underwent CEA after 14 days.⁹ These studies were limited by the small numbers of patients included, and by the use of different definitions of ‘early’ or ‘hyperacute’ surgery timing.

The recent publication by Stromberg *et al.*¹ provides convincing data to settle the question of timing of surgery. The conclusion of their study involving 2,596 patients was that very early CEA, performed within 2 days of an ischaemic event (that is, on the day of symptoms or on either of the following 2 days), has a detrimental effect on outcome. Specifically, the combined mortality and stroke rate in patients undergoing CEA within 2 days was 11.5%, compared with 3.6% for patients treated 3–7 days after their qualifying event, 4.0% for those treated after 8–14 days, and 5.4% for those treated after 15–180 days. Multivariate analysis showed that time to intervention was the strongest determinant of risk of stroke or death, with an odds ratio of 4.24 (95% CI 2.07–8.70, $P < 0.001$) for surgery within 2 days of the ischaemic event compared with surgery on days 3–7.¹ The increased risk was not attributable to a difference between centres, nor to variation in qualifying events (TIA, minor stroke or major stroke) in those undergoing CEA at early or late time points. However, amaurosis fugax (transient monocular blindness) as the qualifying event was independently associated with a lower risk of surgery complications.

The strength of this study is its size: over 2,000 patients were analysed prospectively,¹ compared with earlier publications involving approximately 100 patients.^{8,9} The fact that the results encompass >93% of all CEAs performed in Sweden over a 3-year period (to May 2011), and so are likely to be applicable to a wide range of patients and institutions, is an additional advantage. As such, the results are convincing. The conclusion is that very early surgery, within 48 h of an ischaemic event, should be avoided, but surgery between days 3 and 14 is safe and should remain the target for treatment.

What might be the explanation for the increased risk associated with very early surgery? Previous studies have shown that emergency CEA for an ongoing stroke is associated with a particularly high rate of perioperative stroke,¹⁰ which suggests that the presence of acute thrombus on a recently ruptured plaque could underlie the risk of very early operation. Together with strategies to treat hypertension, 3 days of medical treatment with antiplatelet agents, and possibly statins, are likely to stabilize the carotid plaque, substantially reducing the risks associated with CEA. Ideally, randomized head-to-head trials should be conducted to establish whether the benefits of 3 days’ optimal medical treatment outweigh the risk

of recurrent events while awaiting CEA. In the meantime, guidelines should recommend that CEA be performed between 3 and 14 days after the appearance of symptoms of brain ischaemia.

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Competing interests

The authors declare no competing interests.

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