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REVIEW

Neurological complications of carotid revascularisation

Teddy Y Wu,[1] Neil E Anderson,[1] P Alan Barber[2]

[1]Department of Neurology, Auckland City Hospital, Auckland, New Zealand
[2]Department of Medicine, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand

Correspondence to
Professor P Alan Barber, Department of Medicine, Faculty of Medicine and Health Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand; a.barber@auckland.ac.nz

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ABSTRACT

Carotid endarterectomy (CEA) is an effective treatment for patients with recently symptomatic severe carotid stenosis and in selected patients with symptomatic moderate carotid stenosis. Carotid artery angioplasty and stenting (CAS) is emerging as an alternative to CEA, and randomised controlled trials suggest comparable efficacy to CEA in prevention of non-perioperative stroke. Neurovascular complications can result from both procedures, usually from thromboembolism from the operated vessel, cerebral hypoperfusion causing ischaemia and, rarely, intracerebral haemorrhage. The overall incidence of perioperative strokes complicating CEA and CAS is approximately 4% and 6%, respectively, and represents a devastating outcome that the procedure was designed to prevent. Other neurological sequelae complicating carotid revascularisation include cerebral hyperperfusion syndrome, cranial and peripheral nerve injuries, and contrast encephalopathy in patients undergoing CAS. In this review, we analyse the incidence, mechanisms and perioperative management of neurological complications for patients undergoing carotid revascularisation.

INTRODUCTION

Patients with moderate to severe internal carotid artery (ICA) stenosis are at increased risk of ischaemic stroke. The risk is highest in those patients with recent symptoms. Carotid endarterectomy (CEA) is effective in preventing strokes in symptomatic patients with severe stenosis and in selected patients with moderate stenosis.[1–3] The North American Carotid Endarterectomy Trial (NASCET) reported an absolute risk reduction in ipsilateral ischaemic stroke in patients undergoing CEA of 17% over medical therapy at 2 years. The European Carotid Surgery Trial (ECST) reported an absolute risk reduction of 13.8% in ipsilateral ischaemic stroke at 3 years. Patients with asymptomatic severe carotid artery stenosis may benefit from CEA if perioperative morbidity is minimised. The Asymptomatic Carotid Surgery Trial (ACST) and Endarterectomy for Asymptomatic Carotid Stenosis (ACAS) study reported a net reduction in stroke risk of 5.4% and 5.9%, respectively, over medical therapy over 5 years.[4 5]

Carotid artery angioplasty with stenting (CAS) is a less invasive alternative to CEA. Its use in the treatment of atherosclerotic carotid disease has increased exponentially over the past 2 decades due to its ease of administration and because it can be performed under sedation. CAS has a high procedural success rate in observational studies and stenting registries.[6] Long-term efficacy data from multicentre randomised controlled trials (RCTs), the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis study (EVA-3S) and the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) showed that the frequency of non-perioperative strokes in patients treated with carotid angioplasty was similar to that in those treated with CEA.[7–9]

The major adverse outcome in CEA and CAS is perioperative stroke, the very outcome the procedures are designed to prevent. The rates of procedure related strokes following CEA were 3.3%–6.4% in the symptomatic CEA trials and 1.2%–3.0% in the asymptomatic trials. This was comparable to the perioperative stroke incidence in the CEA arms of the stenting trials. In the major CAS versus CEA trials, CAS had a higher incidence of perioperative stroke, reported to be between 2.5% and 10%.[7 10–14] Other perioperative neurological complications include peripheral and cranial nerve injuries and postoperative encephalopathy.

In this review we analyse the reported incidence, mechanisms and management of perioperative neurological complications following CEA and CAS.

PERIOPERATIVE NEUROVASCULAR COMPLICATIONS

Perioperative neurovascular complications are suspected when a patient wakes with, or develops new, neurological symptoms in the perioperative period, considered to be within 30 days, of CEA or CAS. Table 1 summarises the incidence of perioperative strokes in the major revascularisation trials.

Carotid endarterectomy

In earlier series, the frequency of perioperative mortality was 6.6% and the frequency of stroke was 14.5% following CEA.[17] The reduction in operative morbidity and mortality since these earlier studies is likely due to a combination of improvements in patient selection, surgical techniques and perioperative management. CEA remains the recommended treatment for patients with severe symptomatic carotid stenosis and in selected patients with symptomatic moderate stenosis or asymptomatic severe stenosis.[1–5] The safety and long-term efficacy of CEA in the management of carotid artery disease has been demonstrated in large RCTs.[2 3] Compared with CAS, CEA is associated with improved outcomes for

Table 1 Incidence of perioperative strokes in major carotid revascularisation trials

Trial (year)	Stroke within 30 days of CEA	Stroke within 30 days of CAS	p Value*
Symptomatic			
VA 309[1] (1991)	3/91 (3.3%)	–	–
NASCET[15] (1998)	85/1453 (5.8%)	–	–
ECST[2] (1998)	116/1807 (6.4%)	–	–
EVA-3S[11] (2006)	9/259 (3.5%)	24/261 (9.2%)	0.007
SPACE[13] (2006)	36/584 (6.2%)	45/599 (7.5%)	0.36
ICSS[14] (2010)†	27/821 (3.3%)	58/828 (7.0%)	0.0006
CREST[7] (2010)‡	21/653 (2.3%)	37/668 (5.5%)	0.04
Total	297/5668 (5.2%)	164/2356 (7.0%)	0.003
Asymptomatic			
VA Coop[16] (1993)	6/203 (3.0%)	–	–
ACAS[4] (1996)	10/825 (1.2%)	–	–
ACST[5] (2004)	35/1560 (2.2%)	–	–
CREST[7] (2010)	8/587 (1.4%)	15/594 (2.5%)	0.15
Total	59/3175 (1.9%)	15/594 (2.5%)	0.28
Mixed			
CAVATAS[10] (2001)	22/253 (8.7%)	25/251 (10%)	0.63
SAPPHIRE[12] (2004)	5/167 (3.1%)	6/167 (3.6%)	0.76
Total	27/420 (6.4%)	31/418 (7.4%)	0.57
Overall	383/9263 (4.1%)	210/3368 (6.2%)	<0.0001

All rates are based on intention to treat analysis except ICSS†.
*p Value by χ^2test.
†Per protocol analysis.
‡Within 30 days of procedure if performed within 30 days of randomisation or within 36 days of randomisation if did not undergo procedure within 30 days of randomisation.
CAS, carotid artery angioplasty with stenting; CEA, carotid endarterectomy.

the combined outcome of periprocedural death or stroke, or subsequent stroke, the endpoints used in trials comparing CEA with medical therapy.[18]

CEA involves cross-clamping of the carotid artery before arteriotomy. Depending on the neurological status of the patient during clamping, a shunt may be used to augment cerebral perfusion. Synthetic or venous graft patches can be used over the endarterectomy segment before vessel closure. A heparin bolus is given at the beginning of the procedure to maintain an activated clotting time two to three times that of normal to reduce embolic phenomena. Protamine sulphate can be used to reverse heparin on completion of surgery. The procedure can be performed under general anaesthesia (GA) or with loco-regional anaesthesia (LA).

NASCET, ECST and the Veteran's Affairs (VA) 309 study reported perioperative stroke rates following CEA of 5.8%, 6.4% and 3.3%, respectively.[1 2 15] Most perioperative events were ipsilateral to the operated vessel, ischaemic in origin and considered non-disabling. Death occurred in approximately 10% of patients with perioperative stroke. ACAS, ACST and the asymptomatic VA study reported perioperative stroke rates of 1.2%, 2.2% and 3.0%, respectively.[4 5 16] In the surgical arms of the CEA versus CAS trials, perioperative strokes complicated between 1.4% and 8.7% of CEAs.[7 10–14]

Haemorrhagic strokes and non-ipsilateral cerebral infarcts occurred less frequently than ipsilateral infarcts. The incidence of intracranial haemorrhage following CEA ranges from 0.3% to 2.0%, and in NASCET the 30-day risk of intracranial haemorrhage was 0.64% in surgically treated patients.[19] Most intracerebral haemorrhage (ICH) is due to haemorrhagic transformation of a perioperative ischaemic stroke, while primary ICH and subarachnoid haemorrhage (SAH) usually have a delayed onset after an uneventful postoperative period.[19]

Carotid angioplasty and stenting

Carotid angioplasty and stenting is an alternative to CEA, although its exact place in the treatment of carotid artery disease remains subject to debate.[18] CAS is most successful in the hands of operators with high volume experience.[18 20] CAS is also indicated in patients unsuitable for CEA due to anatomical considerations, those considered at high risk for surgery and where a patient expresses a strong preference for this procedure. CAS is performed by the intra-arterial introduction of a balloon-stent system via a guide wire before balloon angioplasty and stent deployment. Cerebral embolic protection devices may be used. The advantages of CAS are the relative ease of performing it, and because it can be carried out under light sedation. Heparin is given at the beginning of the procedure and can be reversed at completion. Aspirin and clopidogrel are taken preoperatively and continued for at least 30 days after the procedure, at which time either aspirin or clopidogrel alone are continued indefinitely.

CAVATAS was the first RCT to compare the two modalities with 504 patients randomised to either carotid angioplasty or CEA.[10] Twenty-six per cent of the patients in the carotid angioplasty arm received a carotid stent. Twenty-five patients (10%) in the stenting angioplasty arm had perioperative strokes compared with 22 patients (8.7%) in the CEA arm (p=0.63). Most stenting angioplasty related strokes occurred intraoperatively or periprocedurally and all except one patient had ipsilateral cerebral infarction. Three stented angioplasty patients developed fatal ICH outside of the immediate procedural period, presumably due to cerebral hyperperfusion. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE), the Stent-Protected Angioplasty versus Carotid Endarterectomy study (SPACE) and EVA-3S reported periprocedural stroke rates following CAS of 3.6%, 7.5% and 9.2%, respectively, compared with 3.1%, 6.2% and 3.5% in those undergoing CEA.[11–13]

The interim results of the International Carotid Stenting Study (ICSS) and CREST, the two largest RCTs of CEA versus CAS, have been published.[7 14] In ICSS, where patients with symptomatic moderate to severe ICA stenosis were randomised to CAS or CEA, there were 58 (7%) strokes within 30 days of CAS compared to 27 (3.3%) following CEA (p=0.0006).[14] The difference in the 30-day stroke rate was due to more 'non-disabling' strokes in the CAS group (4.3% vs 1.3%, p=0.0002). In CREST, both symptomatic and asymptomatic patients were randomised and the periprocedural stroke rate was also higher in patients treated with CAS than with CEA (CAS 52 (4.1%) vs 29 (2.3%), p=0.01). However, the rate of major periprocedural ipsilateral stroke was not significantly different (CAS 11 (0.9%) vs CEA 4 (0.3%), p=0.09) with an increase in the rate of minor stroke in the CAS arm (CAS 37 (2.9%) vs CEA 17 (1.4%), p=0.009). In symptomatic patients in the CREST study, those treated with CAS were nearly twice as likely to have periprocedural stroke than those treated with CEA (CAS 37 (5.5%) vs CEA 21 (3.2%), p=0.04). In the asymptomatic patients, there was no difference in periprocedural stroke rates between CAS and CEA.[7] Major and minor stroke were found to have an effect on physical health, and minor stroke also had an effect on mental health, at 1 year, whereas the effect of periprocedural myocardial infarction was less certain. ICH occurred following 0.36%–4.5% of the CAS procedures.[21]

Limitations of revascularisation trials

A major shortcoming of trials has been the lack of reporting of the rates of perioperative transient ischaemic attacks (TIA), where up to two thirds of TIA patients have ischaemic change

on magnetic resonance diffusion-weighted imaging (DWI).[22] The reported rates of complications in the major trials are based on clinical syndromes lasting more than 24 h and could have excluded patients with short duration symptoms and evidence of infarction on DWI. Patients may also have cerebral infarction during CEA without awakening with clinical symptoms. A meta-analysis reported an average rate of new post-procedure cerebral ischaemia on DWI of 37% in CAS and 10% in CEA, much higher than the 30-day clinical stroke and death rates of 3.45% and 2.12%, respectively.[23] In the non-randomised ICSS MRI substudy, 50% of the CAS group and 17% of the CEA group had ischaemic change on post-procedural DWI.[24] The sequelae of DWI lesions are uncertain, but small studies have suggested a possible link with long-term neuropsychological deficits.[25]

There is ongoing debate regarding the interpretation of the results and limitations of the major CAS trials.[26 27] Differences exist between the trials in terms of study design, types of stent employed, use of cerebral protection devices (CPDs) (27% in SPACE, 72% in ICSS and >90% in SAPPHIRE, EVA-3S and CREST), postoperative care (including the use of dual anti-platelet therapy) and study outcomes. These factors may influence periprocedural stroke rates. The process of credentialing interventionists in the CAS arms of the trials was, in general, less stringent than for vascular surgeons.[27] The rigorous accreditation of interventionists in CREST may account for the low perioperative complication rate in this trial. Reductions in complication rates have been seen in the CAS arms of trials over time and it is likely that further improvements in devices and in the experience of interventionists will lead to additional improvements.

MECHANISMS OF PERIOPERATIVE STROKES

Thrombosis and embolisation

Approximately two thirds of perioperative ischaemic strokes result from thromboemboli with the majority occurring either during or within the first few days of CEA.[28 29] Intraoperative thromboemboli occur during cross-clamping, arteriotomy, shunt placement and vessel closure by disrupting the atheromatous plaque, and stimulating local platelet activation and aggregation.[28 30 31] In CAS, thromboemboli may arise as a result of plaque disruption at the site of intervention, protrusion of the thrombus through open cell stents with subsequent embolisation, or more proximally from the aortic arch during device introduction.[32] Intimal injury and dissection of vessel walls can occur during shunt insertion. Intimal injury can also occur during the insertion of a CPD.[32] Air embolism can result from shunt introduction in CEA or balloon rupture in CAS. The most common cause of a delayed stroke following an uneventful early postoperative period after CEA is thrombosis of the endarterectomy segment secondary to dissection, uneven suture lines or kinking of the carotid artery.[28 33] Other causes of delayed stroke include arterial spasm and a patient's thrombogenic tendency, but in some cases the cause is unknown.[33] Acute or subacute carotid in-stent thrombosis rarely complicates CAS and is usually the result of inadequate preoperative anti-platelet therapy.[32 34]

Haemodynamic injury

Intraoperative reduction in blood pressure and persistent postoperative hypotension have been suggested by some authors to be risk factors for neurological injury, while others have found no associated risk.[35–38] Perioperative hypotension and bradycardia can occur in up to 75% of patients undergoing carotid revascularisation,[39] and are seen more frequently in CAS than in CEA due to mechanical stretching of the carotid baroreceptors after stent placement.[36] Sympathetic dysfunction is more frequent with CAS and may require use of vasopressors to maintain haemodynamic stability.[40] Risk factors for post-CAS hypotension include lesions involving the carotid bulb, calcified or ulcerated plaque and contralateral disease, while the risk is reduced in patients with previous ipsilateral CEA.[38] Hypotension from baroreceptor manipulation in CEA is usually transient and has not been shown to significantly increase the risk of hypoperfusion injury.[36] General anaesthetic agents may also lead to hypotension as a result of the negative haemodynamic effects of anaesthesia on sympathetic tone, baroreceptor activity and the peripheral vasculature.[41]

Cerebral hypoperfusion may also be caused by deliberate carotid occlusion during clamping in CEA and during balloon dilatation in CAS. Clamping intolerance is largely attributed to hypoperfusion, but can also be caused by thrombosis of intracranial vessels due to distal low flow.[30] Cerebral perfusion distal to clamping is reliant on collateral circulation from the contralateral carotid artery. Patients with contralateral ICA stenosis or occlusion are at an increased risk of clamp intolerance. In CAS, reduction in blood flow due to temporary balloon occlusion of the ICA may reduce washout of downstream embolic debris and decrease collateral flow.[37 42]

Cerebral hypertension can be seen during and following carotid revascularisation in up to 66% of CEA patients and 39% of CAS patients.[41 43] Perioperative hypertension is a result of surgical denervation of the carotid baroreceptors. Baroreceptor dysfunction may persist beyond the perioperative period, although no long-term hypertensive effect has been reported. Postoperative hypertension can exacerbate the expected postoperative increase in cerebral blood flow (CBF) and predispose patients to the cerebral hyperperfusion syndrome (CHS) and ICH.

ICH and disorders of impaired cerebral autoregulation

ICH can occur following 0.3%–2.0% of CEA and 0.36%–4.5% of CAS procedures.[19 21] ICH occurs in three forms: haemorrhagic transformation of an ischaemic stroke, primary ICH and SAH. The risk of haemorrhagic transformation of an ischaemic stroke is increased in patients with a large pre-existing infarct. Extravasation of blood into the infarcted tissue can occur after reperfusion and may lead to neurological deterioration.

Cerebral hyperperfusion syndrome

CHS is defined as an increase in CBF of over 100% compared to baseline, in a patient with new onset headache ipsilateral to the carotid revascularisation, focal neurological deficits and seizures. Postoperative changes in CBF can be determined by transcranial doppler (TCD), perfusion MRI or single photon emission CT. An increase in CBF of 30%–40% over baseline is usually observed after carotid revascularisation and can last for several hours to days.[44] In a subset of patients, the CBF increases by over 100% reaching a maximum 3–4 days postoperatively, but this increase may persist and lead to cerebral oedema or haemorrhage up to 25 days after revascularisation.[19 44 45] The incidence of CHS varies from 0.2% to 18.9% after CEA and from 0.4% to 11.7% after CAS. The wide variation in the incidence of CHS is likely due to differences in the definition of cerebral hyperperfusion and study size, with a reported incidence of less than 3% in larger studies.[21 44] Only 29% of patients with a post-procedure increase in CBF of greater than 100% develop symptoms of CHS.[21]

The postulated mechanism of cerebral hyperperfusion is related to chronic cerebral hypoperfusion before revascularisation. In

patients with severe ICA stenosis, intracranial arteries dilate maximally in response to chronic hypoperfusion; this results in reduced cerebral perfusion reserve and impairment of cerebral autoregulation. With a sustained increase in CBF, disruption of the blood–brain barrier can lead to parenchymal oedema, and subarachnoid or intraparenchymal haemorrhage. Other risk factors for CHS include uncontrolled hypertension, an arterially isolated cerebral hemisphere and contralateral carotid occlusion.[44 46] Postoperative ICH is usually associated with CHS. ICH associated with CHS occurs earlier after CAS than CEA, probably as a result of the more aggressive anti-platelet therapy and increased risk of haemorrhagic transformation associated with intraoperative embolic stroke.[32] ICH associated with CHS carries a poor prognosis with a mortality of approximately 50%, with many of the survivors permanently disabled.[32 44]

Reversible cerebral vasoconstriction syndrome

A rare cause of post-revascularisation cerebral ischaemia is reversible cerebral vasoconstriction syndrome (RCVS), which has been reported in six patients following CEA.[47] To our knowledge no case of RCVS has been reported after CAS. Patients with post-CEA RCVS present within 8 days of the procedure with recurrent thunderclap headache ipsilateral to the CEA and focal neurological deficits. Diagnosis of RCVS requires exclusion of other causes of thunderclap headaches and neurological deficits. The prognosis of RCVS appears to be relatively benign based on the small number of reported cases. There are no RCTs to guide treatment, but nimodipine and verapamil have been reported to be modestly effective in single centre series.[48 49] High dose, short-term prednisone at 1 mg/kg has been recommended with the rationale that steroids may reduce vasoconstriction.[49 50]

Differentiating RCVS and CHS

We, and others, propose that RCVS and CHS following carotid revascularisation are within a spectrum of disorders related to impaired cerebral autoregulation.[51] It is important to distinguish between the two syndromes, because while antihypertensive agents are used to treat RCVS, some agents may increase cerebral perfusion in CHS. There is, however, no evidence from RCTs that antihypertensive agents are harmful. The Lindegaard Index (LI), which is the ratio of ipsilateral middle cerebral artery (MCA) to extracranial ICA blood flow velocities, is used as a measure of the presence and severity of cerebral vasospasm in patients with SAH.[52] Cerebral vasospasm rather than hyperaemia is likely to be present when the LI is greater than 3,[52] but to our knowledge the LI has not been used to distinguish between RCVS and CHS.

CRANIAL AND PERIPHERAL NERVE INJURIES

The proximity of cranial nerves IX, X, XI, XII, the sympathetic chain and cervical nerve roots to the carotid artery predispose these nerves to injury in CEA, either from surgical dissection, traction injury or compression from a cervical haematoma. In CEA, the incidence of nerve injuries is between 3% and 23% in individual series[53] and between 3.9% and 9.5% in the RCTs.[10 11 14–16 53] In NASCET and ECST, 8.6% and 6.3% of patients, respectively, had at least one peripheral nerve injury.[15 53] Hypoglossal nerve injury was the most common cranial nerve injured in CEA. Most patients recovered completely from the nerve injury. A post hoc analysis of ECST identified the duration of the procedure and the use of patch angioplasty as significant risk factors for cranial nerve injury. The OR of nerve injury increased by 1.5 for every 30 min increase in operation time.[53] The risk of cranial or peripheral nerve injury in CAS is negligible. EVA-3S reported one patient with Horner syndrome due to carotid artery dissection after CAS. Two other CAS patients from EVA-3S and one from ICSS had cranial nerve injuries, but all had conversion to open endarterectomy after failed CAS.

NEUROLOGICAL COMPLICATIONS OF ANAESTHESIA

Neurological complications associated with anaesthesia are an important cause of morbidity. General anaesthetic agents can cause haemodynamic fluctuations, seizures and postoperative delirium. Neurological complications of LA include nerve injury from direct needle trauma or compression from a haematoma, and systemic toxicity from inadvertent intravascular injection or overdose from rapid absorption from highly vascularised tissue. Toxicity from local anaesthetic agents can result in excessive sedation, tinnitus and seizures.[54] Seizures are estimated to occur in less than four patients per 1000.[55] The approach to reducing neurological complications associated with anaesthesia includes careful attention to injection technique and avoiding excessive doses of anaesthetic agents.[54]

The General Anaesthesia versus Local Anaesthesia for carotid surgery (GALA) study demonstrated no difference in the perioperative stroke risk between CEA performed under LA or GA.[56] GALA did report a non-significant reduction in perioperative stroke rate in patients with contralateral carotid occlusion who had CEA performed under LA. A meta-analysis of RCTs comparing LA to GA in CEA found no difference in perioperative stroke risk between the two types of anaesthetic technique.[57]

CONTRAST ENCEPHALOPATHY

Contrast encephalopathy is a rare complication of CAS, and is caused by disruption of the blood–brain barrier by the contrast material. Patients typically present with transient visual symptoms, but stroke-like neurological symptoms may occur.[32] Findings on non-contrast CT may resemble SAH with sulcal enhancement.[58] No ischaemic or haemorrhagic change is seen on MRI. The prognosis following contrast encephalopathy is usually benign and full recovery within 48 h is expected. The risk of contrast encephalopathy increases with prolonged procedures.[32]

RISK FACTORS LEADING TO NEUROVASCULAR COMPLICATIONS

Patient factors

Age and symptomatic status are two major patient factors associated with operative risk in CAS.[59 60] In the pooled analysis of ICSS, EVA-3S and SPACE, patients aged 70 years or older treated with CAS had twice the perioperative risk of stroke compared to CAS patients younger than 70 years.[59] In a meta-analysis of over 50 000 CAS procedures, patients with symptomatic carotid disease, or who were 75 years of age or older, or who had a history of hypertension, had an almost twofold increase in the risk of periprocedural stroke.[60]

In contrast to CAS, patients aged 70 years or older who had CEA were not more likely to have perioperative stroke.[59] After CEA, perioperative risk is highest for neurologically unstable patients (such as those with stroke in evolution or crescendo TIAs), women, patients with hemispheric rather than retinal symptoms, and those with occlusion of the contralateral ICA.[15 61 62] It is unclear why there should be a gender difference in perioperative stroke risk, but women tend to have smaller calibre vessels, which may predispose them to post-surgical thrombosis.[61]

Tandem lesions

The presence of intracranial artherosclerotic disease (IAD) increases the long-term stroke risk in medically treated patients due to the negative haemodynamic effect on cerebral perfusion. Carotid clamping in the presence of a distal tandem lesion may increase the risk of thrombosis at the site of the distal lesion due to low flow. However, the presence of a tandem lesion has not been consistently shown to increase complications. Tandem lesions were not associated with increased operative risk in NASCET but they were in ECST.[63 64] In NASCET, the number needed to treat to prevent an ipsilateral stroke at 3 years was half in patients with IAD when compared to patients without tandem IAD. Therefore, in the absence of a definitive increase in operative risk, tandem lesions are not a contraindication for CEA.[63] To our knowledge there is no literature available on the procedural risk with tandem lesions in CAS.

Technical factors

In CEA, the use of patch angioplasty rather than primary closure is associated with lower risk of perioperative stroke.[65] Operator skill also has an impact on the outcome of revascularisation.[18 66] The lead-in phase of CREST suggested operator training affected procedural related complications; neuroradiologists had five times fewer events per 100 CAS procedures than vascular surgeons.[66] The American Heart Association guidelines recommend that procedures for symptomatic stenosis should only be performed by operators with a periprocedural complication rate of 4%–6% or less in CAS and 6% or less in CEA.[67]

PERIOPERATIVE MONITORING AND MANAGEMENT

Perioperative monitoring

Different methods of perioperative cerebral monitoring are used including direct patient monitoring or use of objective surrogates of cerebral ischaemia, in an attempt to reduce the risk of perioperative complications.

Intraoperative monitoring

Direct observation of neurological state during procedures performed under sedation and LA is the most sensitive method for detecting intraoperative events. When revascularisation is performed under GA, assessment of cerebral function during carotid artery clamping can be achieved by 16-lead electroencephalography (EEG), somatosensory evoked potential (SSEP) monitoring, near infrared spectroscopy (NIRS), TCD and stump pressure (SP) measurement.

Neurophysiological monitoring

Cerebral ischaemia is indicated by the development of slow waves and attenuation of α and β activities on EEG, or a >50% reduction of amplitude or increase in central conduction time with SSEP.[68] SSEPs are particularly useful in patients with pre-existing EEG abnormalities. Both methods are sensitive in detecting cerebral ischaemia, but depend on the availability of a neurophysiology technician and equipment.

Non-neurophysiological monitoring

NIRS measures transcranial, regional cerebral oxygenation (rSo_2) from calculation of the mixture of arterial and capillary oxygenation after clamping. A 20% reduction of rSo_2 has a 98% negative predictive value for cerebral ischaemia, but a low positive predictive value and should not be used without concurrent use of EEG or SSEP.[68]

The SP measures the perfusion pressure transmitted around the Circle of Willis during carotid clamping. It has been used to select patients for shunt insertion, but the optimal SP above which shunt insertion is not required is unknown. SP lacks sensitivity when compared to awake neurological monitoring.[69]

TCD measurement of MCA velocity can be used to identify patients at risk of ischaemia or haemorrhage. Ischaemia is considered to be present if ipsilateral MCA velocity is reduced by >60% compared to baseline during clamping.[70] Conversely, an increase in MCA velocity of >100% is indicative of cerebral hyperperfusion and is associated with an increased risk of developing CHS. Anti-hypertensive treatment in patients with hyperperfusion has been shown to reduce the incidence of postoperative ICH.[71] Limitations of TCD include lack of a temporal window in 10%–20% of patients.

Cerebral protection

Shunt insertion

Shunting during carotid clamping theoretically maintains CBF and reduces the risk of ischaemia caused by hypoperfusion.[30] The use of shunting varies widely among surgeons and there is no robust evidence to support or refute its use.[72] Some surgeons routinely use shunts, others are guided by the development of neurological changes during awake endarterectomy or ischaemic changes on cerebral monitoring during clamping, and a minority do not use shunting at all.[72]

Embolic CPD

The aim of a CPD in CAS is to prevent embolic injury during balloon dilatation and stent placement. A systematic review of 134 studies demonstrated a reduced risk of procedural stroke in patients treated with CPD (RR 0.62, 95% CI 0.54 to 0.72).[73] However, SPACE, EVA-3S and two other small RCTs failed to show any benefit associated with use of a CPD.[74 75] Furthermore, patients treated with a CPD have higher rates of postoperative DWI lesions.[24] Until further large RCTs are performed, the use of CPD should be based on local experience and restricted to patients in whom the arterial anatomy allows passage of the device.

Perioperative management

Microembolic signals on TCD ultrasound

Cerebral embolisation can be observed on TCD as microembolic signals (MES). Most MES occur during direct manipulation of the carotid artery and in the first few postoperative hours.[76 77] Perioperative MES have been related to risk of neurological events and new ischaemic lesions on MRI.[76 78 79] High frequency (>50/h) postoperative MES are present in up to 11% of CEA patients and over half of these patients will experience a clinical thromboembolic event.[78]

Haemodynamic management

Hypertension is associated with increased risk of CHS. It is reasonable to delay revascularisation when significant hypertension (systolic pressure >180 mm Hg or diastolic pressure >100 mm Hg) is present. Blood pressure lowering agents with cardioprotective effects such as α or β-blockers are favoured, but judicious titration is required to avoid hypotension in patients with severe ICA stenosis or coronary artery disease.[41] Direct vasodilators such as calcium channel blockers, nitrates, sodium nitroprusside and hydralazine should be avoided postoperatively in anticipation of the postoperative increase in cerebral perfusion.[44] A reasonable postoperative systolic blood pressure target is 140–160 mm Hg, while the mean arterial pressure should be maintained above 60 mm Hg to ensure adequate cerebral perfusion. Intraoperative hypotension should be avoided during

Table 2 Key features of perioperative neurological complications of carotid revascularisation

	Carotid endarterectomy	Carotid artery stenting
Indications	Symptomatic moderate to severe carotid stenosis Severe asymptomatic stenosis	Symptomatic moderate to severe carotid stenosis Severe asymptomatic stenosis. Patients not suitable for CEA
Neurological complications	Strokes: thromboembolism, clamp intolerance, intracerebral haemorrhage, RCVS Cerebral hyperperfusion syndrome Cranial nerve injuries	Strokes: thromboembolic, baroreceptor stretching, intracerebral haemorrhage Cerebral hyperperfusion syndrome Contrast encephalopathy
Perioperative neurological monitoring	Direct neurological observation if LA EEG and SSEP preferred over NIRS and stump pressure TCD monitoring of embolism and cerebral hyperperfusion	Direct neurological observation TCD monitoring as per CEA
Cerebral protection	Shunt insertion during carotid clamping	Cerebral protection device but emerging evidence that use increases embolisation
Management	► Stroke: – Ischaemic, neurovascular imaging and consider carotid re-exploration if thrombosis of endarterectomy segment. Consider mechanical thrombectomy if distal embolisation – Haemorrhagic, rapid BP control and aim for systolic BP <140 mm Hg ► Cerebral hyperperfusion syndrome: aim for systolic BP <140 mm Hg or preoperative baseline ► Cerebral vasoconstriction: nimodipine or verapamil ► Nerve injuries—exclude local haematoma+expectant	► Stroke: – Ischaemia, neurovascular imaging+consider endovascular treatment with thrombolysis, thromboaspiration or thrombectomy – Haemorrhagic: as per CEA – Cerebral hyperperfusion syndrome: as per CEA – Cerebral vasoconstriction: as per CEA – Contrast encephalopathy—expectant

BP, blood pressure; CEA, carotid endarterectomy; CNS, central nervous system; EEG, electroencephalography; LA, loco-regional anaesthesia; NIRS, near infrared spectroscopy; RCVS, reversible cerebral vasoconstriction syndrome; SSEP, somatosensory evoked potentials; TCD, transcranial doppler.

cross-clamping in CEA and following balloon dilatation and stent insertion in CAS. Intraoperative hypotension may be treated with fluid challenge or a vasopressor,[41] but treatment must be tailored to an individual's co-morbidities as pharmacologically induced hypertension may trigger coronary ischaemia. The decision to treat postoperative hypotension should be made with consideration of the patient's risk of cerebral hyperperfusion. Myocardial ischaemia, myocardial dysfunction and arrhythmias should be considered in patients with perioperative hypotension.

Other adjunctive and anticoagulation therapy

A heparin bolus is routinely given at the beginning of CEA and CAS to reduce the risk of thromboembolic events. The effects of heparin can be reversed with protamine sulphate to minimise the risk of a cervical or access site haematoma. There were fears that the use of protamine would increase the risk of a thrombotic stroke in CEA, but there was no significant increase in the risk of perioperative stroke with protamine use in a non-randomised substudy in GALA.[80]

Anti-platelet therapy should be taken by patients with carotid artery disease and is usually continued indefinitely. Treatment with aspirin and clopidogrel before CEA reduces postoperative MES on TCD,[81] but the potential benefit of this combination in reducing postoperative ischaemic strokes has not been assessed in RCTs.

Dextran, a polysaccharide compound with an anti-adhesion effect on platelets on vascular grafts, has been used to reduce perioperative strokes. In phase 1 of the Dextran in Carotid Endarterectomy (DICE) trial, where treatment was started before arteriotomy and continued for 16 h, dextran reduced postoperative TCD detected MES when compared to placebo.[82] In phase 2 of DICE, 687 patients were randomised to receive dextran or placebo, and dextran resulted in a non-significant 28% reduction in the odds of perioperative ipsilateral stroke, witnessed TIA or stroke death.[83] The rate of postoperative MES may be used to guide dextran therapy. The optimal MES frequency at which to initiate therapy has not been defined, although a threshold of 25 MES per 10 min has been used.[77]

S-nitroso-glutathione (SNG), which releases endothelium-derived nitric oxide with antiplatelet activity, is an alternative agent for reducing TCD detected MES. Postoperative therapy with SNG significantly reduced MES after CEA and CAS in two small RCTs, but these trials were not powered to detect reductions in postoperative ischaemic events.[84 85] To our knowledge, there is no current or planned RCT investigating the potential benefit of SNG on post-revascularisation stroke. In the absence of firm evidence, the indications for the use of these agents should depend on local practice guidelines.

MANAGEMENT OF POSTOPERATIVE STROKE

In CEA, most postoperative strokes are due to thrombosis of the operated ICA causing partial or complete occlusion at the site of the endarterectomy. There is no robust evidence that immediate re-operation improves outcome, but some authors believe it reduces the risk of irreversible cerebral damage.[28 29] In NASCET, five of 13 patients who had re-operation for carotid occlusion derived benefit, and in general only about half of re-operated patients achieve a good functional outcome.[15 28 29]

When a patient develops neurological symptoms during CAS, direct angiographic visualisation can determine the cause and site of thromboembolism. Acute or subacute in-stent thrombosis is a rare (0.5%–2%) complication of CAS and is usually due to lack of pre-treatment with dual antiplatelet therapy.[34] Different techniques are available to treat perioperative thromboembolism including mechanical thromboembolectomy, thrombus fragmentation and microaspiration, and intra-arterial thrombolysis. The administration of glycoprotein platelet inhibitors (abciximab or tirofiban) or 'facilitated thrombolysis' (intra-arterial thrombolysis followed by half dose abciximab) can achieve recanalisation.[34] If medical therapy is unsuccessful, surgical thrombectomy with or without stent removal can be considered.

MANAGEMENT OF CHS

In patients with CHS, strict and rapid blood pressure control using agents such as labetalol and clonidine that do not dilate the cerebral vasculature should be considered. Some authors have suggested anti-hypertensive agents with direct cerebral vasodilatory effects, such as sodium nitroprusside, glycerol trinitrate and dihydropyridine calcium channel blockers, should not be used in CHS.[44] However, this has not been tested in RCTs and the key to the management of CHS is likely to be rapid blood pressure control rather than the class of agent used. Treatment should be continued until the systolic blood pressure is less than 140 mm Hg and cerebral hyperperfusion resolves.[21 44] The duration of treatment can be guided by serial measurements of MCA velocity with TCD until cerebral autoregulation is restored, although some authors have recommended treatment for 6 months.[44] Patients with seizures should be treated with anticonvulsants and prophylactic anticonvulsants can be considered in those with periodic lateralised epileptiform discharges.[86] No specific recommendation can be made regarding the choice of anticonvulsant therapy. Treatment of cerebral oedema may include sedation, mannitol, hypertonic saline and steroids, but the effect of these treatments on clinical outcome is uncertain.[21 44] Patients and physicians should be aware of the risk of CHS and the need for prompt presentation if symptoms develop. Patients with elevated intracranial pressure and CHS should be managed by physicians with experience in neurocritical care.

CONCLUSION

Carotid revascularisation with CEA or CAS can lead to neurological complications, with perioperative stroke being the most devastating outcome. The key features of the neurological complications related to carotid revascularisation are summarised in table 2. The incidence of procedure related stroke has consistently been shown to be less in patients treated with CEA than with CAS, but the two procedures have similar long-term efficacy. CEA remains the treatment modality with the most robust evidence for the treatment of recently symptomatic severe carotid stenosis and in selected patients with symptomatic moderate carotid stenosis. In centres with a low rate of procedural complications, CAS is a reasonable alternative in patients not suitable for CEA or younger patients with a preference for a non-operative approach. An evidence-based approach to optimal perioperative management in reducing operative stroke risk is not firmly established, but it is imperative to ensure tight haemodynamic control and correct treatable causes of cerebral ischaemia. In patients developing postoperative neurological deficits, urgent cerebral and neurovascular imaging is vital to guide subsequent management in both interventions.

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Neurological complications of carotid revascularisation

Teddy Y Wu, Neil E Anderson and P Alan Barber

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