There is More to Preventing Stroke After Carotid Surgery than Shunt and Patch Debates

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“We are too much accustomed to attribute to a single cause, that which is the product of several, and the majority of our controversies come from that”

Baron Justus von Leibig (1803–1873).

Summary

Despite level I evidence that carotid endarterectomy (CEA) confers significant benefit over ‘best medical therapy’, the paradox remains that the very operation undertaken to prevent stroke (in the long-term) is associated with a small, but important risk of stroke in the peri-operative period. This paradox has, of course, been recognised for more than 50 years. However, the debate as to how stroke and other cardiovascular complications might be prevented following CEA remains largely unresolved and has been inappropriately dominated by ‘single-issue’ subjects. These include; choice of anaesthesia, traditional versus eversion endarterectomy, dose of aspirin, shunt usage, shunt thresholds, patching, tacking sutures, peri-operative monitoring, sinus nerve blockade and heparin reversal. Many of these issues are now largely irrelevant, already resolved or simply unresolvable. Their enduring persistence has, however, compromised the evolution of newer and more novel strategies for reducing peri-operative cardiovascular morbidity and mortality.

The ‘hottest’ single-issue subject of the moment is the role of locoregional anaesthesia (LRA) versus general anaesthesia. The literature abounds with claims that CEA under LRA confers significant benefit, but a 2004 meta-analysis of the seven available randomised trials continues to show no significant difference in outcome. However, a systematic review of the 41 non-randomised trials showed that CEA under LRA conferred significant reductions in: (i) any stroke (2.0 versus 4.8%), (ii) death/any stroke (2.4 versus 5.8%), (iii) myocardial infarction (1.1 versus 3.3%), (iv) pulmonary complications (0.4 versus 2.1%) and (v) a reduced requirement for shunting (13.3 versus 49.5%). Fortunately, this is one of the few single-issue subjects where a large, well-designed randomised trial (GALA) is underway and will certainly guide practice in the future.

However, advocates of LRA must also recognise that while CEA under LRA is undoubtedly the ‘gold-standard’ for predicting who needs a shunt, haemodynamic failure is actually responsible for 20% of all intra-operative strokes. Accordingly, reliance upon LRA (for general quality control or monitoring) will not prevent the other 80% of thromboembolic intra-operative strokes and few (if any) of the post-operative ones, unless they are associated with post-endarterectomy hypertension. Some other monitoring or quality control strategy will be required to achieve this goal. Accordingly, the most important future benefit of CEA under LRA may be the potential for significantly reducing early cardiovascular morbidity, especially hypertension. In that respect, alone, the data from GALA will assume considerable importance. Until then, the available evidence suggests that surgeons can perform CEA under either LRA or general anaesthesia according to individual preference.

The choice/dose of antiplatelet agent and whether

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it should be stopped pre-operatively is another enduring controversy. This debate largely arose because a subgroup analysis of the NASCET database suggested that CEA patients receiving low dose aspirin (<325 mg daily) incurred a higher operative risk (6.9 versus 1.8%) compared with patients receiving higher doses (650–1300 mg). In response to this unplanned secondary analysis, the ACES study randomised >2500 patients and showed the converse to be true. More importantly (especially from a practical point of view), an increasing proportion of cardiovascular patients are now prescribed chronic Clopidogrel therapy (sometimes in combination with aspirin). This is largely due to the small, but significant reduction in vascular death and/or non-fatal stroke/MI observed in the CAPRIE study. However, the recently published MATCH study (clopidogrel alone versus aspirin+clopidogrel in patients with a prior history of stroke/TIA) has shown that chronic combination antiplatelet therapy does not reduce the long-term risk of stroke, but does increase the risk of life-threatening bleeding. This is an important finding because chronic Clopidogrel usage trebles the bleeding time, while aspirin and clopidogrel (in combination) confers a five-fold increase. Accordingly, much of the debate regarding the choice and dose of antiplatelet therapy is largely resolved. Low dose aspirin remains the first-line agent in CEA patients and aspirin should not be stopped prior to surgery or be replaced with warfarin. Combination aspirin and clopidogrel therapy should generally be avoided and any patient receiving chronic Clopidogrel (on its own) should probably stop this medication at least 7 days before CEA and resume aspirin therapy wherever possible.

The most enduring single-issue subject, however, remains the role of shunting. Few randomised trials have been performed, most have been methodologically flawed, so that meaningful interpretation of the data is all but impossible. Few surgeons now advocate a policy of ‘never’ shunting, so that the battle lines are drawn between the ‘routine’ and ‘selective’ shunters, whose differences are now virtually irreconcilable. So who is on the side of the righteous? In fact, if one critically analyses the rationales underlying shunting, the debate is actually fairly straightforward. If you truly believe in a policy of selective shunting, then the only method for ensuring that you have reliably identified patients at risk of haemodynamic failure during carotid clamping is to perform CEA under LRA. No other monitoring modality can (or will) accurately predict who needs a shunt and surgeons, quite simply, have to accept this unpalatable fact. Accordingly, unless the surgeon is motivated towards changing practice towards performing CEA under LRA (which seems the most obvious strategy for selective shunters), it is probably safer to advocate a policy of routine shunting. Arguments that shunting is a regular cause of intimal injury or that shunts impede access etc. are largely over-exaggerated by the pro-LRA lobby. As far as this author is concerned, the shunt debate has inappropriately dominated practice to the detriment of virtually everything else. There are other, far more important, factors that influence the operative risk. On a par with the intensity of the shunt debate is the parallel controversy regarding the role of patching. Moreover, having touched on the subject of patching, one inevitably raises the question as to whether eversion endarterectomy should be the preferred option. Despite its enduring nature, there is more evidence-based data to guide practice in this area. The 2004 Cochrane Overview clearly shows that a policy of routine patching is significantly preferable to routine primary closure. Routine patching conferred a three to fourfold reduction in peri-operative stroke/thrombosis and late stroke/restenosis and there was no evidence that patch type (prosthetic, vein) influenced outcome. Thus, for those surgeons who seek to modify surgical practice (based on evidence), the case for always closing the arteriotomy primarily cannot now be sustained. Accordingly (as with the shunt debate), the real argument is whether the arteriotomy should be patched selectively or routinely. No randomised trial has ever addressed this question, simply because it remains totally impossible to get a group of surgeons to agree consensus criteria for selective patching!

Surgeons must, therefore, make their own decision and accept that this is probably another issue that is never going to be resolved scientifically. Although, (by training) I am a routine patcher, intuitively I have to accept that not everyone needs a patch. However, unlike the invaluable (and otherwise infallible) role of LRA for guiding selective shunt deployment, the surgeon has no reliable way of knowing which patients should be patched or not. Moreover, as with the shunt debate, arguments that the risks of vein patch rupture or patch infection mitigate against patching are largely over-stated. These risks (<1% overall) have to be compared with the systematic evidence demonstrating the much higher risks of early thrombosis and late stroke associated with primary closure. Finally, provided the arteriotomy is closed with a patch, systematic reviews of the randomised trials show that early and long-term outcomes (stroke, restenosis etc.) are not improved by eversion endarterectomy. Thus, one can reasonably conclude that, with
the exception of advocating a policy of routine primary closure, surgeons can patch the arteriotomy selectively or routinely (with whatever patch material they prefer) or perform an eversion endarterectomy, in the knowledge that they cannot be criticised on the currently available evidence.

Sinus nerve blockade is another enduring controversy. Four randomised trials have now addressed this question, but their findings (to-date) have hardly influenced clinical practice. Only one found that sinus nerve blockade significantly reduced intra-operative variations in blood pressure. Unfortunately, this study was limited by only randomising 40 patients and there was no data regarding blood pressure control in the early post-operative period. Three other studies showed no evidence of any significant reduction in the incidence of intra-operative hypotension requiring treatment though, paradoxically, the lowest blood pressures were seen in patients undergoing sinus nerve division. Two studies observed that patients randomised to sinus nerve blockade were more likely to suffer hypertension in the early post-operative period, presumably following sinus reinnervation. Accordingly, there is really no debate any more. There is no systematic evidence supporting the routine use of sinus nerve blockade in modern carotid surgical practice and sinus nerve division should be avoided.

Another longstanding debate is whether heparin should be reversed following flow restoration. As recently as 1994, 54% of US surgeons and 26% of European surgeons routinely administered protamine at the end of arterial reconstructions. Only one randomised trial has attempted to answer this question during CEA (suspended after recruiting 65 patients). Although, neck drain losses were significantly reduced in protamine-reversed patients, this study was abandoned because three strokes followed early post-operative carotid thrombosis in protamine-reversed patients, in whom no technical error was identified at re-exploration. Although one occurred in a non-randomised patient, the authors felt that it was unethical to continue. A number of non-randomised studies have reported contradictory findings regarding haematoma formation, but two have reported an increased risk of stroke in protamine-reversed patients. More recently, the GALA Investigators have performed an interim analysis on the use of heparin-reversal in 938 patients in the study. This showed that outcomes (peri-operative stroke, death, haematoma, re-exploration) were no different. Accordingly, although the overall data are not particularly robust, the available evidence suggests that there is no systematic evidence that routine heparin-reversal is beneficial to the CEA patient. Surgeons can, however, administer protamine (selectively) according to individual preference.

The final controversy, and one which this author thinks has been inappropriately lost amid the battle-field of shunt/patch debates, is the role of peri-operative monitoring and quality control assessment. It seems slightly ridiculous that vascular surgeons will spend up to 4 h doing a femoro-distal bypass and check that everything is technically satisfactory using completion angiography and then not apply the same principle to CEA. This is despite increasing awareness that inadvertent technical error complicates up to two-thirds of all peri-operative strokes, second, there is often not much one can do once the stroke has occurred and third, the outcomes are frequently devastating and ultimately irreversible.

To-date, no randomised trials have been performed, largely because there is no agreement as to what constitutes the most appropriate monitoring policy. There are a number of reasons why no consensus has emerged. First, virtually every monitoring modality has been used to develop thresholds for shunting, even though haemodynamic failure is a relatively rare cause of intra-operative stroke. With the exception of transcranial Doppler (TCD), none have been developed to identify embolisation, which is now accepted to be the principal cause of peri-operative stroke. Second, is the naive assumption that there must be one single and ‘all superior’ monitoring modality to the exclusion of all others. Third (and most important) is a simple failure to ask the right questions. For example, CEA under LRA will undoubtedly prevent haemodynamic failure during carotid clamping (because that is an appropriate question to ask of it). However, it will neither prevent stroke due to embolisation of luminal thrombus following restoration of flow, nor early post-operative thrombosis. In our centre, we were surprised to observe that the majority of intra-operative strokes followed embolisation of thrombus adherent to the endarterectomy zone following flow restoration (despite irrigation and venting). The source of these thrombi was found to be bleeding from the vasa vasorum on to the highly thrombogenic endarterectomy zone. Having recognised this, intra-operative stroke has now been virtually abolished by simply adding completion angiography to our intra-operative monitoring protocol. Again, ask the important question and tailor monitoring and quality control modalities accordingly. Similarly, stroke due to post-operative carotid thrombosis (POCT) complicates 2–3% of CEAs worldwide and was previously thought to be unpreventable. However, research from a number of centres around
the world has now shown that there is a 1–2 h period of increasing embolisation before the onset of any neurological deficit. Accordingly, detection of high rate embolisation (using TCD) might enable this ‘window of opportunity’ to be exploited pharmacologically (e.g. incremental Dextran therapy) so as to prevent progression onto thrombosis and major stroke. More recent evidence also suggests that POCT might even be prevented in the future by the administration of a single 75 mg dose of clopidogrel (in addition to regular aspirin) the night before surgery. This is because the platelets of patients with higher rates of embolisation following CEA appear to be more sensitive to ADP. Accordingly, with higher rates of embolisation following CEA surgery. This is because the platelets of patients before (in addition to regular aspirin) the night.

In summary, in the five decades since CEA was first introduced, the debate about how to reduce the operative risk has been totally dominated by ‘single-issue’ subjects. Clearly some are important, but many are now either irrelevant or not solvable. More importantly, their enduring persistence has prevented other more useful practices and strategies from emerging. To this author, the ‘hot topics’ are: (i) establishing whether CEA under LRA reduces early cardiovascular morbidity (especially hypertension), (ii) evaluating the role of dual antiplatelet therapy immediately prior to surgery in preventing POCT and (iii) defining the role of targeted monitoring and quality control. Out in the cold should be consigned (iii) defining the role of targeted monitoring and establishing whether CEA under LRA reduces early cardiovascular morbidity (especially hypertension), (ii) evaluating the role of dual antiplatelet therapy immediately prior to surgery in preventing POCT and (iii) defining the role of targeted monitoring and quality control. Out in the cold should be consigned.

References

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