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REVIEW

# Intracerebral Haemorrhage Following Carotid Endarterectomy

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***Objectives.*** *To determine risk factors for the development of hyperperfusion and intra-cerebral haemorrhage following carotid endarterectomy and formulate potential protocols for prevention.*
***Methods.*** *MEDLINE database search of the English language literature (1966–2002) was performed using the words 'cerebral haemorrhage', 'intracranial haemorrhage' and 'carotid endarterectomy'. Other articles were cross-referenced by hand.*
***Results.*** *There are no data from randomised trials confirming the significance of any single risk factor. The evidence suggests that the following may have a role: pre-operative hypertension, recent ipsilateral non-haemorrhagic stroke, previous ischaemic cerebral infarction, surgery for a >90% ipsilateral internal carotid artery (ICA) stenosis, impaired cerebrovascular reserve, intra-operative haemodynamic or embolic ischaemia, post-operative hypertension, an ipsilateral increase of ≥175% in peak middle cerebral artery velocity (MCAV) and/or a ≥100% increase in pulsatility index.*
***Conclusions.*** *A critical ICA stenosis with impaired cerebrovascular reserve resulting in maximal intracerebral vasodilatation and post-operative hyperperfusion (impaired autoregulation) appear to be central to the development of ICH. Appropriate pre-operative screening and post-operative monitoring in high risk patients might identify those who would benefit from manipulation of the haemodynamic events that appear to promote ICH.*

*Key Words: Endarterectomy; Carotid; Intracranial hemorrhage; Cerebral hemorrhage; Post-operative complications.*

## Introduction

Following publication of the ECST[1] and NASCET[2] trials carotid endarterectomy (CEA) has been performed with increasing frequency.[3] Although these trials showed that surgery is better than best medical therapy for stroke prevention in patients with a symptomatic critical ICA stenosis the combined data from these, and the VA Trial indicate a 30-day stroke or death rate for CEA of 7.1%.[4] Current interest has, therefore, focused on improving the risk-benefit of surgery by reducing the number of peri-operative neurological events.

Strategies by which ischaemic or embolic peri-operative strokes may be reduced include routine patching,[5,6] intra-operative quality control,[7] post-operative monitoring with transcranial Doppler (TCD) and intervention for multiple embolic events[8] and the performance of CEA under regional rather than general anaesthesia.[9] The latter is currently the subject of an international randomised trial (The GALA Trial). There is also evidence suggesting that the risks associated with CEA are reduced when surgery is performed by surgeons, or in units, with a high annual workload.[10,11]

Despite the promising results of studies that have assessed the benefit of these techniques in reducing peri-operative ischaemic strokes the incidence of haemorrhagic stroke (intracerebral haemorrhage—ICH) following CEA has remained constant (0.25–1.8%).[12,13] Thus, ICH has assumed increasing significance in the pathogenesis of peri-operative neurological complications. Furthermore ICH may also occur following carotid angioplasty and stenting.[14–17]

A number of risk factors that might increase the risk of post-CEA ICH have been suggested including recent cerebral infarction, hypertension, a high-grade carotid stenosis, impaired cerebrovascular reserve, post-reperfusion hyperaemia and anticoagulant

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**Table 1. Prevalence of risk factors in 86 patients presenting with post-CEA intracerebral haemorrhage**

| Risk factor | Present | Absent | Not documented |
|---|---|---|---|
| Ipsilateral CT infarct or neurological deficit | 25/83 (30%) | 58/83 (70%) | 3/86 (3%) |
| Ipsilateral carotid stenosis >90% | 62/69 (90%) | 7/69 (10%) | 17/86 (20%) |
| Contralateral carotid occlusion | 16/59 (27%) | 43/59 (73%) | 27/86 (31%) |
| Hypertension | 40/82 (49%) | 41/82 (51%) | 4/86 (5%) |
| Intra-operative BP >160/90 mmHg | 15/22 (68%) | 7/22 (32%) | 64/86 (74%) |
| Post-operative BP >160/90 mmHg | 28/62 (45%) | 34/62 (55%) | 24/86 (28%) |
| General anaesthesia | 41/44 (93%) | 3/44 (7%) | 42/86 (49%) |
| Shunt | 28/43 (65%) | 15/43 (35%) | 43/86 (50%) |
| Peri-operative anticoagulation | 31/58 (53%) | 27/58 (47%) | 28/86 (33%) |

therapy. However, the relative importance of these remains uncertain. This review will, therefore, examine the evidence for each and propose protocols for their identification and management.

## Methods

A Medline review of the English language literature (1966–2002) was performed using the words 'cerebral haemorrhage', 'intracranial haemorrhage' and 'carotid endarterectomy'. Other articles were cross-referenced by hand.

## Results

### *Incidence and presentation*

Sixteen reports in the English language literature identified 103 cases of ICH complicating 20,197 CEAs, an overall incidence of 0.51%.[7,12,13,18–30] From these, and nine case reports, detailed information was available on 86 cases.[18–22,24–28,31–39] This data is summarised in Table 1. The median age of affected patients was 64 (range: 42–81) years and although there was a greater proportion of females (41M:43F) this may reflect publication bias since it was not evident from the larger series reporting the incidence of ICH.[29,30] The median duration from surgery to haemorrhage was 4 days (range: intraoperative—25 days) and this was associated with a 67% mortality.

Patients who suffer ICH often have an unremarkable early post-operative course, are normotensive and have no neurological deficit.[21] The most common initial symptom is a severe, unilateral frontal or temporal headache (35%) followed, perhaps after several days, by seizures associated with an abrupt rise in systemic blood pressure (17%), the development of a neurological deficit (47%) and coma (44%).

### *Pre-operative risk factors*

*Cerebral infarction*

In 1963 Bruetman reported six cases of ICH following CEA in patients with a persisting neurological deficit or EEG evidence of cerebral infarction.[21] Subsequently Wylie reported 5 cases of ICH in nine patients undergoing operation within one week of stroke, concluding that following cerebral infarction there was a critical period during which an increase in cerebral perfusion pressure could cause serious or fatal intracranial haemorrhage adjacent to the area of infarction.[24] More recent reports using either computerised tomography (CT) or autopsy confirm that ICH occurs in areas of pre-operative cerebral infarction.[19,21,22,24,26,31,33]

However, ICH also occurs in normal brain parenchyma irrespective of the presence or absence of infarction in other areas of the brain.[19,25,36] Similarly, in an animal model of cerebral ischaemia reversal within 50 minutes resulted in anaemic cerebral infarction whilst longer periods of ischaemia were associated with cerebral haemorrhage following reperfusion. The authors postulated that ischaemia leads to softening of brain tissue and vessel wall damage with rupture of the latter, and thus haemorrhage, on resumption of cerebral blood flow.[40]

Post-ischaemic damage to the terminal cerebral vascular net, characterised by perivascular oedema and clumping of erythrocytes and platelets within venules and arterioles, was also demonstrated by Meyer and Denny-Brown.[41] Small vessel changes were particularly noted in the watershed area of ischaemia and restoration of flow to these damaged vessels promoted diapedesis and peri-vascular haemorrhage. Although anticoagulants increased flow rates by reducing erythrocyte and platelet aggregation, they resulted in more severe haemorrhage.

Finally, it has also been suggested that peri-operative embolic events may increase the risk of cerebral injury. Subsequent fragmentation of emboli or relaxation of vascular spasm promotes distal move-

ment of the embolus and exposure of the previously ischaemic tissue to the full force of systolic blood pressure causing haemorrhage from damaged capillaries.[42]

Twenty-seven (31%) of the ICH cases described in detail had been evaluated by pre-operative cerebral CT. Of these 11/27 (41%) showed no infarction, 12/27 (44%) ipsilateral infarction, and 4/27 (15%) infarction contralateral to the hemisphere with a subsequent ICH.

In summary, although a significant proportion of patients who develop ICH have a previous cerebral infarction a similar proportion do not. However, early CEA following ischaemic stroke may promote ICH and the timing of CEA in patients referred for surgery after stroke is controversial. The relative risks to the patient are those of a further neurological event caused by an unstable carotid plaque or post-operative ICH. Unfortunately, there are no guidelines that will balance the risk of these conflicting hazards although CT evidence of infarction, a progressive neurological deficit and reduced conscious level appear to increase the risk of early CEA for acute stroke.[43]

*Pre-operative cerebral hypoperfusion and impaired cerebrovascular reserve*

Of all the factors proposed as promoting ICH a high-grade ipsilateral carotid artery stenosis is the most consistent finding.[19,25,27–29,32,44] A >90% stenosis was present in 90% of patients, 27% of whom also had a contralateral occlusion. Poor collateralisation was also noted on cerebral angiography in one of these studies.[27]

The mechanism by which a high grade stenosis imposes a risk of ICH has been explained on the basis of the 'normal perfusion pressure breakthrough' theory described by Spetzler.[45] Although this hypothesis explained the occurrence of ICH following surgery for intracerebral AV malformations it is equally applicable to patients with severe carotid disease. In a hemisphere that is chronically ischaemic secondary to steal by an arteriovenous fistula, autoregulation is impaired and the distal arterial network becomes chronically dilated, thus ensuring maximal blood flow. When normal flow is re-establishing after removal or occlusion of the fistula luxury perfusion occurs due to failure of autoregulation in the dilated vessels. This leads to cerebral oedema and haemorrhage. It has also been suggested that the cerebral microcirculation is unusually susceptible to injury after a prolonged period with a reduced perfusion pressure.[32] This theory is supported by the work of Sundt who demonstrated reduced baseline cerebral blood flow in five patients who developed ICH compared to other patients with similar stenoses and clinical risk factors who made an uneventful recovery from CEA.[46]

Patients with pre-operative hypoperfusion and impaired cerebrovascular reserve can be identified prior to CEA by TCD measurement of middle cerebral artery velocity (MCAV) before and after administration of a cerebral vasodilator such as inspired $CO_2$ or acetazolamide. Thus Sbarigia *et al*. were able to show that patients in whom the MCAV did not increase after acetazolamide, presumably due to paralysis of autoregulation and maximal arteriolar vasodilatation, developed symptomatic cerebral hyperperfusion after surgery.[47]

*Bilateral carotid disease*

Information on the severity of bilateral disease was available in 60 patients. Of these 28/60 (47%) had a combined stenosis of >160%. In a further 10 patients collateralisation from the contralateral side was described as poor (7), moderate (1), or good (2). Thus 50% of patients developing ICH had either combined stenoses of >160% or poor collateral flow. Unfortunately, there are no data available on frequency of this pattern of bilateral carotid disease in patients who do not develop ICH.

*Hypertension*

Caplan first proposed hypertension as a cause of ICH, describing two patients with significant pre-operative hypertension which became more severe post-operatively and was followed by ICH.[33] This suggestion has been endorsed by several other authors.[20–22,30,35] Further evidence of a role for acute hypertension is available from autopsy studies and post-CEA cerebral CT scans which show features similar to those of malignant hypertension (swelling and hyperplasia of endothelial cells, vascular necrosis, extravasation of erythrocytes, fibrin exudates, marked cerebral oedema) in patients suffering ICH.[18,25,26,29,32,33,39] From other work it is apparent that a combination of hypertension and patent collateral vessels are required to invoke experimental haemorrhagic infarction.[50]

There is some evidence to suggest that poorly controlled pre-existing hypertension may also be of relevance. Thus autopsy studies have shown that longstanding hypertension is associated with the development of intracerebral arteriolar microaneurysms[52,53] and the occurrence of small intracerebral haemorrhages at the junction of cortical grey and white matter. The increased susceptibility of hypertensives

to ICH could be secondary to small vessel changes and aneurysm rupture. This risk is likely to be further increased by uncontrolled post-CEA hyperaemia in patients with impaired cerebrovascular reserve and a failure of normal autoregulation.

The possible mechanisms by which pre-existing hypertension might increase the risk of ICH has been examined in animal studies. Thus in an experimental model of renal hypertension in monkeys persistent segmental cerebral arteriolar spasm with stasis and segmentation of blood was noted and brain histology demonstrated arteriolonecrosis and cerebral fibrinoid arteriolosclerosis.[49] These changes were associated with areas of ICH. Subsequently, Hardin, using an identical animal model, was able to prevent haemorrhagic infarction, at the expense of ischaemic infarction, by administration of intravenous low molecular weight dextran (LMWD) both before and after induction of ischaemia. He concluded that vascular stasis, sludging and anoxic changes affecting both the vessel wall and surrounding parenchyma played a major role in the pathogenesis of haemorrhagic infarction.[51] The protective effect of LMWD appeared to be related to its indirect action of preventing further anoxic damage to the vessel wall, and surrounding parenchyma, perhaps by increasing microcirculatory blood flow.

Finally, the effect of hypertension on cerebral blood flow (CBF) has been assessed in both non-ischaemic and ischaemic cerebral cortex. In the former CBF remains relatively constant despite changes in blood pressure whilst in ischaemic cortex CBF is directly influenced by systemic blood pressure during periods of both hypotension and normotension. Although increased CBF is not a direct result of hypertension, ischaemia impairs vascular reactivity with or without maximal dilatation[54] thus reducing vascular resistance. This effect may be enhanced by intracellular acidosis which further increases CBF in reperfused ischaemic cortex.[55]

The association between peri-operative hypertension and ICH is not conclusive and of the studies reviewed here in which sufficient information is provided, 40/82 (49%) patients were hypertensive whilst 41/82 (51%) had normal pre-operative blood pressures, no history of post-CEA hypertension and no autopsy changes consistent with malignant hypertension.[24,31,46] The incidence of hypertension in this cohort is similar to that reported for patients in the NASCET Study[2] and this must raise doubts as to the impact of hypertension on the development of post-CEA ICH.

If there is a link between pre-operative hypertension and ICH this may simply reflect cerebral hypoperfusion and an impaired cerebrovascular reserve rather than being a risk factor in its own right. Indeed, induced hypertension in monkeys following occlusion of the middle cerebral artery results in a pronounced increase in regional perfusion pressure[56] suggesting that hypertension may be beneficial in reducing the risk of pre-operative stroke due to hypoperfusion. Thus vigorous antihypertensive therapy prior to surgery may be hazardous. Conversely, hypertension might be considered as a marker of increased risk for ICH in patients who have suffered a previous cerebral infarction or who have an impaired cerebrovascular reserve.

### *Intra-operative risk factors*

#### *Anaesthetic method*

When CEA is performed under local or regional anaesthesia a significant increase in systemic blood pressure occurs after application of the carotid clamps.[57] This is associated with a spontaneous recovery in the initial fall in parameters of cerebral oxygenation. This presumably reflects simultaneous intra-cerebral vasodilatation. If these changes persist during reperfusion the risk of ICH might be increased.

Conversely, when general anaesthesia is used for CEA cerebral oxygenation does not recover after clamping the carotid vessels, perhaps increasing the risk of ischaemic infarction. Review of detailed case reports indicated that 41/86 patients had a general anaesthetic and 3/86 local or regional anaesthesia. The method of anaesthesia was not documented in 42 patients. In the 16 series reports reviewed the proportions of local/regional anaesthesia compared to general anaesthesia in patients who did not develop ICH was not described.

Thus, at present, it is not possible to draw any conclusions as to influence of general or local anaesthesia upon the incidence of ICH. The ongoing GALA Trial (an international randomised trial of general versus local anaesthesia for CEA) should provide further information on this issue.

#### *Operative technique*

Low cerebrovascular reserve with reduced flow from the contralateral hemisphere should be associated with a low mean stump pressure. Despite this, there is no evidence that measurement of stump pressure predicts at-risk patients, although the stump pressure ratio (initial mean stump pressure/pre-occlusion mean arterial pressure) may be of value.[58] Similarly, when a selective policy for shunt insertion is adopted based upon an assessment (direct or indirect) of

cerebral blood flow or function there is tentative evidence that patients requiring a shunt may have a higher risk of ICH. Thus, Jansen reported that a shunt was deployed in 3/5 (60%) and 48/228 (21%) patients who did or did not develop ICH. There is no reason to believe that the shunt itself had any influence upon the occurrence of ICH.

Review of the data from the 86 ICH patients in whom more detailed information was available indicated that 28 patients required a shunt and 15 did not. No data was available for the other 43 patients. In view of the missing data and a general failure to report the reasons for shunt insertion (routine or selective) no useful conclusions can be drawn.

Finally, there is experimental evidence that implicates a role for both peri-operative haemodynamic ischaemia and embolisation in the pathogenesis of some cases of ICH.[42,59] Thus it is logical to suggest that the strategies that minimise these risks (outlined above), together with appropriate intra-operative monitoring to detect their occurrence should be employed. In respect of the latter awake neurological testing during CEA under local/regional anaesthesia, together with TCD monitoring of middle cerebral artery blood flow (emboli detection) would seem the most appropriate methods.

*Intra-operative monitoring*

Various techniques have been employed to identify cerebral hypoperfusion after carotid cross clamping. These depend on the measurement of haemodynamic parameters (stump pressure, middle cerebral artery velocity [MCAV]), parameters of cerebral oxygenation (near infrared spectroscopy, jugular venous blood $O_2$ saturation) or cerebral function (EEG, somatosensory evoked potentials, awake neurological testing). Their main function is to identify, with varying sensitivity and specificity, those patients who require a shunt. As discussed earlier a low stump pressure does not have any predictive value for the development of ICH. Similarly, the benefit of EEG in this role has also been examined with negative results.[21,22,25,26,37] The value of other monitoring modalities has not been critically assessed.

There is some evidence that close monitoring of peri-operative blood pressure changes may be helpful. Thus, of 20 patients with ICH where intraoperative blood pressure was documented 14 showed a rise of $>40$ mmHg in systolic blood pressure above pre-operative levels, one a rise of $<40$ mmHg, and five no change.[19,20,25,31,33,37,39]

Several authors have also shown that post-CEA changes in cerebral blood flow or MCAV predict patients at risk of both hyperperfusion and ICH. Thus, Sundt *et al*. reported that cerebral blood flow may increase by as much as 200% in patients who subsequently developed neurological complications.[46] More recently, Henderson *et al*. showed that $>60$% of patients who suffered an ICH had a $>100$% increase in cerebral blood flow post-operatively.[30]

Other authors have suggested that TCD monitoring has a role in the detection and evaluation of post-CEA hyperperfusion.[23,48] Similarly, Jansen *et al*., using a combination of a $\geq 175$% increase in peak MCAV and a pulsatility index increase $\geq 100$% reported that the positive predictive value, negative predictive value, sensitivity and specificity for developing ICH were 100, 99, 80 and 100%, respectively.[13] These data appear highly promising and thus measures that might reverse these changes could have a major role in reducing the incidence of post-CEA ICH.

*Anticoagulation*

Administration of intra- and post-operative antiplatelet agents and anticoagulants have been implicated in the pathogenesis of ICH by several authors[19,27,30] and Meyer and Denny-Brown showed that anticoagulation promoted ICH in an experimental model.[41] However, the majority of endarterectomies are performed using both intra-operative heparin and post-operative antiplatelet therapy making it difficult to substantiate the role of these agents in promoting ICH. In this respect Poisik *et al*. failed to show a link between fixed-dose heparin therapy during CEA and ICH.[60]

Further, the Mayo Clinic asymptomatic carotid endarterectomy trial was stopped early due to a higher rate of myocardial events in patients randomised to receive no antiplatelet therapy.[61] Similarly, anticoagulants prolong patient survival post-CEA, probably by reducing coronary events.[62] In this latter study, there was no difference in the frequency of cerebral events between patients receiving anticoagulants/antiplatelet drugs and those who did not although the precise nature of the neurological events was not specified.

In summary, although these drugs may increase haemorrhage once it has started they almost certainly do not initiate ICH. Further, it appears that the increased risk of morbidity without their use outweighs any potential risk.

## *Post-operative risk factors*

*Hypertension*

An abrupt elevation in blood pressure frequently occurs in association with the onset of neurological

symptoms in patients with ICH and often follows a period of normotension. It is difficult know whether this is important in the pathogenesis of ICH or if it is a normal response to a sudden rise in intracranial pressure. Nevertheless, it is advisable to institute aggressive anti-hypertensive therapy if such a rise occurs.

## Discussion

From this review a number of factors appear to be associated with an increased risk of ICH following CEA. These are:

1. Pre-operative hypertension.
2. Recent ipsilateral non-haemorrhagic stroke.
3. Previous ischaemic cerebral infarction.
4. >90% stenosis of the ICA for operation.
5. Severe bilateral disease or a contralateral ICA occlusion.
6. Impaired cerebrovascular reserve.
7. Haemodynamic or embolic intra-operative ischaemia.
8. ≥175% increase in peak MCAV on transcranial Doppler assessment of ipsilateral middle cerebral artery flow velocities and/or a pulsatility index ≥100%.
9. >200% increase in cerebral blood flow.
10. Post-operative hypertension.

Unfortunately, it is not possible to determine the overall statistical significance of these potential risk factors from the studies retrieved during our literature review. This would require data on the incidence of these risk factors not only in patients developing ICH but also those suffering an ischaemic stroke and those who did not develop a neurological complication. This information is not available in the majority of publications.

### *Potential interventions for patients believed to be at high risk for ICH*

Although active intervention for pre-operative hypertension could be potentially harmful, particularly in patients with a critical stenosis it would seem sensible to intervene in patients developing post-operative hypertension. When this is required antihypertensives causing vasodilatation should be avoided and rapid control of hypertension achieved by intravenous administration of a β-blocker such as labetolol.

Whilst there are no direct interventions that diminish the risk of ICH associated with previous cerebral infarction, the timing of surgery following a recent stroke requires consideration. Cerebral autoregulatory responses to $CO_2$ recover 3–4 weeks after cerebral infarction yet disautoregulation following induced hypertension may continue for up to 2 months after a stroke.[63] Although initial reports suggested that the risk of ICH following CEA in patients with acute stroke was as high as 60%[64] later studies indicated that the risk in patients with non-disabling stroke was no different whether CEA is performed within 30 days of symptoms or delayed beyond this time.[65,66] Conversely, patients with evolving neurological signs[67] or associated comorbidity (ASA III or IV)[68] have an increased risk when CEA is performed within 3 weeks. A recent review has suggested that surgery might be expedited in patients who make a rapid recovery from their stroke and who have a relatively small infarct on CT whereas in those with larger infarcts and a significant residual neurological deficit surgery should be deferred for 6–8 weeks.[69]

In patients with severe ICA disease the risk of ICH appears to be associated with impaired cerebrovascular reserve. This can be assessed by measuring changes in MCAV before and after acetazolamide or $CO_2$ using TCD. If it is not practical to determine this in all patients prior to CEA then those at risk are likely to be patients with a ≥90% ICA stenosis, a >70% stenosis in association with a contralateral occlusion, or bilateral stenoses of >80%.

Although there is no data to indicate the appropriate management for patients with an impaired reserve following reperfusion it would be logical to monitor both the MCAV and pulsatility index. If these parameters exceed the limits indicated above then steps should be taken to normalise them. Logically, promotion of intra-cerebral vasoconstriction should reverse the abnormal flow associated with hyperperfusion. Methods by which this might be achieved include a period of hypocarbic ventilation if the MCAV or pulsatility index are significantly elevated at the end of surgery or administration of drugs such as β-blockers although the role of the latter is conjectural. These measures should be continued until the haemodynamic abnormalities stabilise below the apparently 'critical' levels described earlier. The 5-HT 1B/1D receptor agonist sumatriptan attenuates experimentally induced cerebral hyperperfusion in both rat[70] and baboon[71] models, whilst having no effect on blood flow at normal flow volumes. In patients with migraine it causes vasoconstriction of the internal carotid and middle cerebral arteries[72,73] without inducing changes in systemic cardiovascular parameters. Thus sumatriptan may reduce the cer-

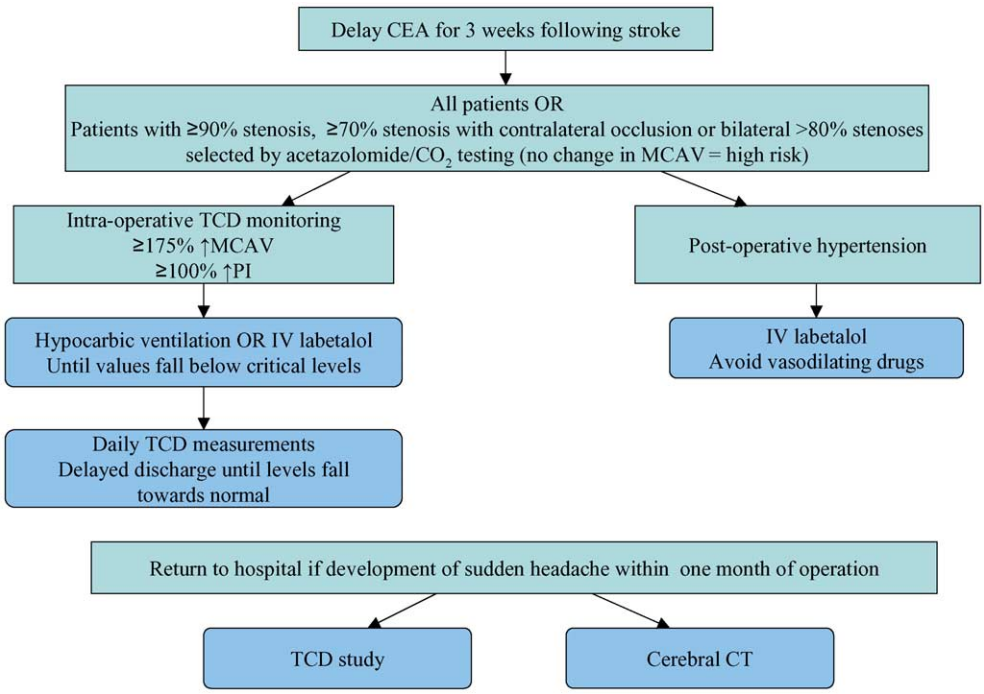


**Fig. 1.** Schematic diagram of suggested protocols for reducing the risk of ICH.

ebral hyperperfusion preceding ICH. None of these strategies have been critically assessed following CEA. Given the relatively low incidence of ICH, initial studies should probably assess the physiological effect of these manoeuvres in a cohort of CEA patients. Although it would be attractive to subsequently perform a randomised study to investigate the role of the most promising methods the relatively low incidence of ICH means such an investigation would require a large multi-centre trial.

Finally, discharge should be delayed for high risk patients until the MCAV and pulsatility index, which should be measured on a daily basis, have started to fall towards normal levels.

Following discharge patients should be advised to return to hospital immediately if they develop a severe headache within the first month of surgery whereupon a TCD study and cerebral CT scan should be performed.

The suggested protocols for reducing the risk of ICH are summarised in Fig. 1.

## Summary

ICH is the most serious manifestation of post-CEA cerebral hyperperfusion, the latter being promoted by an impaired cerebrovascular reserve with maximal dilatation of intracerebral vessels and failure of cerebral autoregulation. Pre-operative screening and post-endarterectomy monitoring of high risk patients might identify those who would benefit from manipulation of the haemodynamic events that appear to promote ICH. Further research is required to confirm the hypotheses outlined in this review and to formulate appropriate pharmacological protocols to reduce the risk of an adverse neurological event. Such manoeuvres might play an important role in reducing the morbidity and mortality of surgery given the implementation of other strategies that make carotid endarterectomy safer.

Finally, the problems of hyperperfusion and ICH will be equally important for patients treated by endovascular methods for carotid disease.

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