Clinical review

Evidence based case report

Should a patient with primary intracerebral haemorrhage receive antiplatelet or anticoagulant therapy?

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Patients with primary intracranial haemorrhage may have risk factors for future thromboembolic events. Such a situation presents a therapeutic dilemma, as illustrated by the following case. A 55 year old man was admitted with right sided weakness. His history included hypertension that was difficult to control, type 2 diabetes, angina, and hyperlipidaemia. He had also had a minor stroke affecting his right side about 10 years previously. He was taking medication: aspirin 75 mg, atorvastatin 10 mg, bendroflumethiazide 2.5 mg, ramipril 2.5 mg, amlodipine 5 mg, isosorbide mononitrate modified release 60 mg, pioglitazone 15 mg (all once a day); hydralazine 50 mg twice a day; and metformin 850 mg and methyldopa 250 mg three times a day. He had smoked 20-30 cigarettes a day most of his adult life until 10 yeas previously, and he drank alcohol in moderation.

Examination confirmed grade 4/5 weakness of his right arm and leg and dysarthria. He was rather obese, with a body mass index of 36. Blood pressure on admission was 200/125 mm Hg, which settled very quickly, however, at about 140/80 mm Hg once the dose of amlodipine was increased to 10 mg once daily.

Electrocardiography showed sinus rhythm and mild left ventricular hypertrophy (voltage criteria). A computed tomogram of the head about 90 hours after the onset of symptoms showed a deep left basal ganglia haematoma (fig 1).

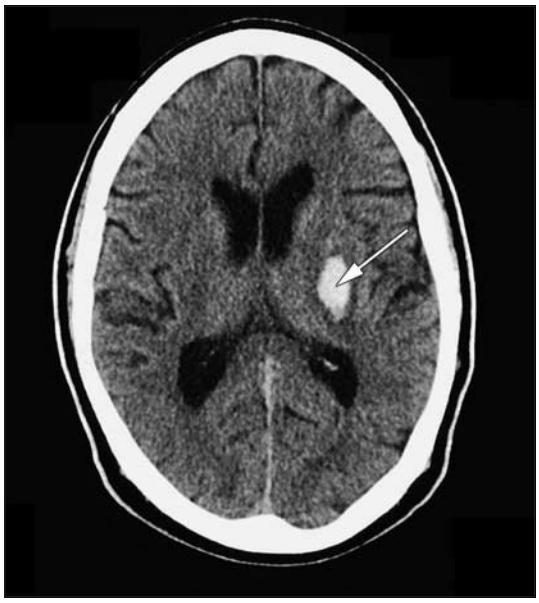

Fig 1 Computed tomogram of the head showing left basal ganglia haematoma (arrowed)

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Should he resume his antiplatelet therapy?

This case raised an important question which is often ignored in practice. Should a patient who seems to have a high thromboembolic risk but is recovering from a potentially fatal intracranial haemorrhage receive antiplatelet agents to prevent future ischaemic (cerebrovascular and other vascular) events? Is there any evidence in favour of or against such therapy?

Search strategy and results

We searched Medline, PubMed, and the Cochrane database for studies that have looked into risk of ischaemic stroke in patients who have had a primary intracerebral haemorrhage; the use of antiplatelet agents in these patients; and the benefits and risks of such therapy.

The literature on these questions was very limited. Most studies were individual observational studies. We found one systemic review on recurrence of stroke after intracranial haemorrhage and no randomised controlled studies on the use of antiplatelet agents. One study, however, systemically reviewed the published controlled trials in which antithrombotics were used after intracranial haemorrhage.

Antiplatelet therapy is well established in secondary prevention of cardiovascular and cerebrovascular disease.[1] Use of antiplatelets is usually avoided in patients who have had an intracranial haemorrhage. Risk of ischaemic stroke in patients who have had a primary intracerebral haemorrhage is not very well established. An annual recurrence risk of 4% to 15% of all stroke types after a primary intracerebral haemorrhage has been reported.[2 3 w1 w2] A systemic review showed most recurrences to be haemorrhages (2.4% a year: intracranial haemorrhage; 1.1% a year: ischaemic

Extra references (w1-w44) are on bmj.com

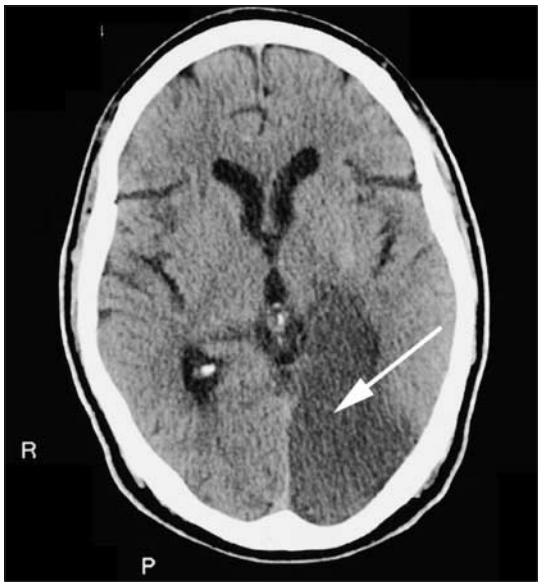

Fig 2 Computed tomogram of the head showing left posterior cerebral artery infarction (arrowed)

stroke).[3] However, there is probably a subgroup (or subgroups) of people at risk of ischaemic stroke—for example, those with a history of smoking, hypertension, diabetes, hyperlipidaemia, or ischaemic heart disease (such as our case). Use of antiplatelets in these patients remains controversial. An increase in intracranial haemorrhage has been reported with aspirin,[4] and aspirin is generally avoided. A systemic review supported neither benefit nor safety from the scant data available, with the conclusion that antithrombotics should be avoided where possible in patients with previous intracranial haemorrhage.[5] None of the studies included in the review was primarily designed to answer the question we were asking.

What other measures reduce risk of stroke in such patients?

We also looked at other risk factors, which, if managed adequately, could reduce the risk of all kinds of stroke recurrences. A meta-analysis of individual data for one million adults in 61 prospective studies showed a very strong relation between usual blood pressure and vascular mortality, including haemorrhagic and ischaemic strokes throughout middle and old age.[6] Importantly the study showed a continuous risk throughout, even with normal blood pressure as far down as at least 115/75 mm Hg. The association of blood pressure and stroke seems to be even stronger in the eastern Asian study, which also estimated a reduction of strokes by a third through a very modest 3 mm Hg population-wide reduction in blood pressure.[7] Hypertension in particular seems to have an important role in causing deep intracranial haemorrhage.[w3-w5] Treatment of high blood pressure has significantly reduced the incidence of primary intracerebral haemorrhage over the past few decades.[w5] Untreated hypertension carries a very high risk of haemorrhagic stroke, which could be reduced by a quarter with treatment.[w4] And patients with primary intracerebral haemorrhage are more likely to rebleed if they have poorly controlled blood pressure.[w6 w7] Adequate control of high blood pressure[8 w8 w9] and other common accompanying risk factors (such as smoking and diabetes[w7 w10]) may reduce recurrence of both haemorrhagic and ischaemic stroke. Use of antiplatelets could provide added benefit in this group. The problem is that very few data exist about the risk of recurrent intracerebral haemorrhage in patients receiving aspirin or warfarin after having a primary intracerebral haemorrhage.[5 9] However, aspirin, which has a lower risk than warfarin,[4 5] may be a reasonable option for patients with deep intracerebral haemorrhage with a high thromboembolic risk.[10] Deep intracerebral haemorrhage seems to have a lower recurrence rate than the lobar haemorrhage.[3]

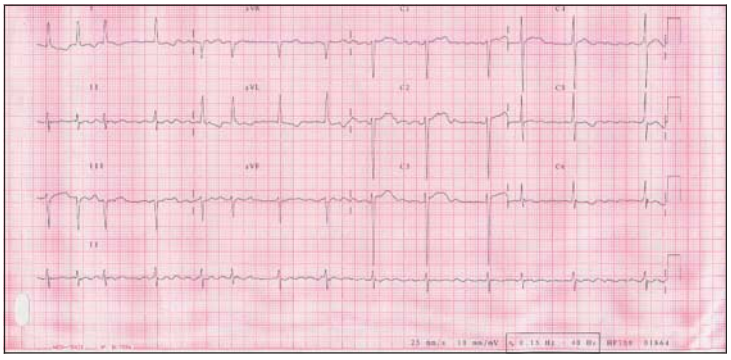

Fig 3 Electrocardiogram showing atrial fibrillation

Case progression

Aspirin was stopped. Blood pressure stayed around 120/70 mm Hg with adjustment of antihypertensive therapy and addition of indapamide and perindopril combined. The patient recovered and was independent within three months.

After discharge from hospital, however, his blood pressure once again became a problem (ambulatory blood pressure monitor recorded systolic readings around 200 mm Hg and diastolic around 120 mm Hg). He was admitted to hospital for investigations for any underlying cause and for better control of his blood pressure. There was protein (0.8 g/l) and glucose, but no blood, in his urine. Urinary catecholamines were within the normal range. Ultrasonography of the abdomen showed normal sized kidneys. His blood pressure quickly settled to within an acceptable range (systolic 120-150 mm Hg; diastolic 70-90 mm Hg). His diabetes was better controlled (haemoglobin A_{1c} 6.8%; normal range 3.5-5.4%). A physician colleague believed that the patient had a very high thromboembolic risk and therefore started dipyridamole 200 mg twice daily about six months after the stroke. We recognise the lack of evidence to support this antiplatelet agent in preference to aspirin in this particular situation.[w11 w12]

About 14 months after the haemorrhagic stroke he was readmitted with a very dense right sided weakness. He had homonymous hemianopia and showed severe neglect of his right side. Blood pressure was 220/125 mm Hg. He remained drowsy (14/15 on the Glasgow coma scale) for several days.

Computed tomography of the head, performed within 24 hours, showed a large area of low attenuation in the left occipital and medial aspect of the parietal lobe—consistent with left posterior cerebral artery infarction (fig 2). He also had atrial fibrillation (fig 3).

Should anticoagulation be used?

Search strategy and results

We again searched Medline, PubMed, and the Cochrane database. We came across many systemic reviews about the risk of thromboembolism in non-valvular atrial fibrillation and relative benefits and risks of anticoagulation versus antiplatelet agents. But we found none for patients who had had previous primary intracerebral haemorrhage. Non-valvular atrial fibrillation carries a fivefold risk of thromboembolism, especially stroke.[11] Elderly patients and those with previous thromboembolism, heart failure, ischaemic heart disease, hypertension, or diabetes are particularly at high risk.[12 13] Anticoagulation is significantly better than aspirin in preventing future vascular events.[14 w13 w14]

The benefit of anticoagulation has to be weighed against the serious risks of bleeding.[w15] The annual rate of major bleeding in a selected trial population whose anticoagulation was carefully monitored was 1.3% a year.[13] Clearly, this is an underestimate and does not reflect true risk in an ordinary non-trial population, and indeed some studies have reported fivefold to 10-fold increases in intracranial haemorrhage in a general population.[w16 w17] Risk of bleeding increases with age and higher intensity of anticoagulation.[15 w18 w19] Several schemes for classifying risk of stroke have been suggested to help identify patients most at risk and therefore most likely to benefit from anticoagulation, but the schemes vary considerably.[13 w20-w23]

Patients with primary intracerebral haemorrhage and atrial fibrillation may be at a higher risk of ischaemic rather than haemorrhagic stroke, and the decision to treat with anticoagulation becomes even more difficult. Currently no clear evidence based guidance is available to help doctors decide whether anticoagulation is appropriate in these patients. In practice, anticoagulants are generally avoided in patients who have previously had intracranial haemorrhage even when they are at risk from thromboembolism in the future. The possibility of bleeding, especially intracranial haemorrhage, is the major reason for avoiding anticoagulant therapy.[16]

Eckman et al used a decision making model (Markov state transition decision model) [w24] to measure quality adjusted life years (QALYs) with or without anticoagulation therapy in a base case of a 69 old man with a history of primary intracerebral haemorrhage and newly diagnosed non-valvular atrial fibrillation.[10] They concluded that survivors of lobar primary intracerebral haemorrhage with non-valvular atrial fibrillation were better off by 1.9 more QALYs without anticoagulation (5.44 years *v* 3.54 years). The same applied to most patients with deep intracranial haemorrhage and atrial fibrillation, although a subgroup may particularly be at high risk of thromboembolic stroke and/or at low risk of recurrence of intracranial haemorrhagia and therefore may benefit from long term anticoagulation or aspirin. However, the study has been criticised [w25] for the assumption of a 15% recurrence rate after index lobar intracranial haemorrhage on the basis of a single study[w2]—very much higher than the 0.0%-5.7% rates reported in other studies.[2 3] Likewise, some observational studies found no differential recurrence rate according to the site of index haemorrhage, which again was low—at 2.1% a year—although a threefold increase in recurrent intracranial haemorrhagia in patients on warfarin was also observed.[9] The rate of recurrence of stroke also seems to vary from 1.0% to 8.9%, depending on risk factors such as hypertension, diabetes, previous stroke, or a transient ischaemic attack,[13] rather than just the site of initial bleeding.

Measures for minimising risk of haemorrhage

Amyloid angiopathy seems to play a dominant role in the pathophysiology of lobar primary intracerebral haemorrhage, especially in older people.[17] Clinically asymptomatic haemorrhagic lesions as identified by magnetic resonance imaging techniques such as gradient echo imaging could serve as a substrate for larger haemorrhages in patients taking warfarin.[18 w26-w28]

Patients taking warfarin could be identified as high risk for intracranial haemorrhage (for example, advanced age, hypertension, prior ischaemic stroke, diabetes, concomitant use of antiplatelets and multiple drugs, intensity of anticoagulation, presence of prosthetic valves, and alcohol use)[19 w29 w30] and therefore be monitored very closely.

Genotype characterisation (apolipoprotein E; e2 and e4 alleles) could identify those at high risk of developing lobar primary intracerebral haemorrhage.[20 w2 w31] Similarly, genetic polymorphism could also identify patients at increased sensitivity to warfarin and hence in need of very close monitoring.[w32 w33] Oral anticoagulants of the future, such as ximelagatran (an oral direct thrombin inhibitor), could help further by avoiding peaks and troughs in international normalised ratio and therefore reduce bleeding risk (at least theoretically) as well as providing sustained protection.[21 w34]

The importance of keeping blood pressure well under control has already been emphasised.

When is best time to start antithrombotic therapy?

Search and results

We again searched Medline, PubMed, and the Cochrane database. Timing of anticoagulation after an intracerebral haemorrhage or even an ischaemic stroke poses further dilemma. Observational studies with small numbers have drawn conflicting conclusions in relation to the use of early anticoagulation (within 48 hours) in high risk embolic strokes (rheumatic heart disease or atrial fibrillation).[w35 w36] Early use of heparin in patients with acute ischaemic stroke and atrial fibrillation was associated with unacceptable bleeding complications in the international stroke trial and the Norwegian HEAST study.[22 23 w37] Secondary prevention studies of atrial fibrillation have included mostly patients with transient ischaemic attack or minor stroke, who probably do not have the same risk of intracerebral haemorrhage as those with more severe stroke.

The possibility of haemorrhagic transformation of an ischaemic infarct—which seems to be a natural consequence of recanalisation (spontaneous or induced by thrombolysis)—complicates matters further, and this is a major concern in the use of thrombolysis. The haemorrhagic stroke in our patient could well have been a secondary transformation rather than a primary intracerebral haemorrhage. The rate of haemorrhagic

transformation seems to be higher in cardioembolic stroke.[w38 w39] Whether asymptomatic haemorrhagic transformation significantly influences early or long term outcome is debatable. Conversion of asymptomatic haemorrhagic transformation into symptomatic intracerebral haemorrhage with early anticoagulation, however, would be a legitimate concern. Factors leading to haemorrhagic transformation (for example, duration of ischaemia, speed of recanalisation, baseline neurological status, and demographic and imaging characteristics) may help in the timing of anticoagulation in the future.[w40 w41] There is some information but no randomised controlled trials about resuming anticoagulation in patients with intracerebral haemorrhage and prosthetic heart valves.[24 w42-w44] There is no information on how soon anticoagulation could be started safely, if at all, in patients with atrial fibrillation after intracerebral haemorrhage.

Outcome

After our patient's intracerebral haemorrhage, we identified control of blood pressure and diabetes as the areas needing most attention. Overall compliance rather than truly "difficult to control" hypertension seemed to be the problem.

We started him on warfarin two weeks after the second (ischaemic) stroke while recognising that he was a very high risk both for future thromboembolism and for intracerebral haemorrhage and therefore would need very close monitoring. He did not make any substantial functional recovery and needed care in a nursing home. However, lately he has been showing some signs of improvement. His blood pressure, international normalised ratio, and diabetes are being regularly monitored. Supervision in the care home has improved compliance with medication.

We acknowledge the lack of evidence for prescribing dipyridamole in preference to aspirin. We also recognise that the area is full of uncertainties, and owing to lack of clear evidence we have not been able to manage the dilemmas with full confidence. We hope that the debate generated by this case might focus researchers' attention on this very important area. We need large scale, well designed trials to help us advise our patients more appropriately in this particularly complex situation.

Contributors: The patient was managed by all authors. MW had the idea of submitting the report. EN and MW conducted the literature search. All authors prepared the manuscript. MW is the guarantor.

Competing interests: None declared.

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Corrections and clarifications

Hajj: journey of a lifetime

In this Clinical Review by Abdul Rashid Gatrad and Aziz Sheikh, the dosage given for a vaccine was incorrect (*BMJ* 2005;330:133-7). The article said that pilgrims to the Hajj in Mecca have to be vaccinated against meningitis before attending—but the vaccine named, ACWY Vax, should be given only once (not twice, as was stated).

Researcher fined for shredding records

In this item in the In Brief column of the News section (*BMJ* 2005;331:8, 2 Jul), we said that Christopher Gillberg, an expert on attention-deficit/hyperactivity disorder in Sweden, had been fined for shredding his research data. In fact, he had been fined for "misuse of office" for his role in failing to comply with a court order granting access to his data (see bmj.com, 23 Jul 2005, News Extra).

UK stops short of outright smoking ban in enclosed public places

Devolution has again tripped us up. This News article by Kaye McIntosh, should have clarified that it is England and Wales (not the whole of the United Kingdom) that have "stopped short of banning smoking in all enclosed public places" (*BMJ* 2005;330:1468, 25 Jun). In Scotland a ban on smoking in public places is scheduled to be introduced in 2006. Northern Ireland is planning to introduce a ban on smoking in public places, but is still undecided on whether the ban will be total or partial.