

Acute Haemorrhagic Stroke

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ABSTRACT

Objective: To review the management and some of the recent advances in acute haemorrhagic stroke.

Data sources: Articles and published reviews on acute haemorrhagic stroke.

Summary of review: Hypertensive intracerebral haemorrhage or subarachnoid haemorrhage (SAH) from a ruptured intracranial saccular aneurysm are the commonest causes for an acute haemorrhagic stroke. Both lesions are often clinically characterised by a sudden severe headache and vomiting with the remaining neurological features dependent on the site of the lesion. The diagnosis requires an urgent non-contrast cerebral computed tomography (CT) scan and a lumbar puncture if the CT scan fails to demonstrate intracranial blood.

Treatment of both intracerebral haemorrhage and SAH includes resuscitation (e.g. cardiovascular and respiratory support) and preventative therapy (e.g. maintaining hydration and nutrition, and preventing aspiration and pressure sores, etc). Further management of an intracerebral haemorrhage by removing the clot is only beneficial if it is near the surface (although stereotactic catheter insertion and infusion of thrombolytics have been used with variable success with deeper haematoma) and if there are signs of intracerebral shift or compression of vital structures (e.g. cerebellar haematoma).

Management of SAH still requires nimodipine and early angiography with surgery to reduce the incidence of cerebral vasospasm and rebleeding, respectively. While intravascular techniques using the Guglielmi detachable coil have improved the outcome in surgically inaccessible (and accessible) aneurysms, management of resistant cerebral vasospasm using 'triple H' therapy (i.e. hypertension, hypervolaemia and haemodilution), intraarterial papaverine, angioplasty, and intrathecal tPA, have not been uniformly successful.

Conclusions: Acute haemorrhagic stroke requires an urgent non-contrast cerebral CT scan for diagnosis. Treatment of an intracerebral haematoma requires evacuation of the clot if accessible and if it is causing an intracerebral shift or compression of vital structures. Nimodipine and urgent surgery to reduce the incidence of cerebral vasospasm and rebleeding, respectively, are standard for the management of a patient with a SAH. While recent advances in intravascular techniques using the Guglielmi detachable coil hold promise, successful management of resistant cerebral vasospasm remains elusive. (**Critical Care and Resuscitation 2000; 2: 209-219**)

Key Words: Acute haemorrhagic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, thrombolysis, Guglielmi detachable coil

Subarachnoid haemorrhage from a ruptured intracranial saccular aneurysm, hypertensive intracerebral haemorrhage, cerebral haemorrhage caused by AV

malformations, mycotic aneurysm, trauma, neoplasms, and coagulation disorders account for most cerebral haemorrhages that present as a stroke. This review will

consider the current management and some of the recent advances in acute spontaneous intracerebral haemorrhage and subarachnoid haemorrhage due to ruptured intracranial saccular aneurysms.

ACUTE INTRACEREBRAL HAEMORRHAGE

Spontaneous haemorrhage into the cerebral parenchyma accounts for approximately 15% of intracerebral haemorrhages, 60% of which occur in the putamen and adjacent internal capsule and thalamus, 20% in the pons and 10% in the cerebellum, the remaining involve temporal, frontal, parietal or occipital lobes. The majority are due to the effects of chronic hypertension on intracranial perforating arteries. However, spontaneous intracerebral haemorrhage can also be caused by vascular malformations, mycotic aneurysms, vasculitis, amyloid angiopathy, amphetamines, cocaine, tumors or coagulopathy (e.g. fibrinolytic therapy, thrombocytopenia, anticoagulants).¹ Rupture and seepage of blood into the ventricular system may also occur. If there are no coagulation abnormalities, then, unlike intracranial saccular aneurysms, rebleeding is rare.

Clinical features

The disorder has an abrupt onset and evolves steadily over minutes, commonly reaching a maximum at 1 hr, although it can evolve over 24 hr.¹ Normally, the onset occurs while the patient is awake and active and only rarely occurs during sleep. A severe headache occurs in 50% cases and the patient often vomits. If subarachnoid bleeding occurs, signs of meningism appear. The site of haemorrhage influences the clinical presentation. For example:

Putamenal haemorrhage. This tends to disrupt the adjacent internal capsule causing slurred speech and contralateral hemiplegia, with the eyes deviating away from the side of the hemiparesis. If the haemorrhage is large, coma can occur within minutes.

Thalamic haemorrhage. This produces a contralateral hemiplegia due to internal capsule involvement, a sensory deficit and skew deviation or a characteristic deviation of both eyes downward and inward with unequal pupils.

Pontine haemorrhage. This causes a quadraplegia, decerebrate rigidity and coma with small pupils that react to light and usually develops over a few minutes. Brain death may occur within hours.

Cerebellar haemorrhage. Clinical signs usually develop over hours with an occipital headache, dizziness, vertigo, repeated vomiting and an inability to stand or walk. Paresis of conjugate lateral gaze toward the side of the haemorrhage, ocular bobbing and skew deviation of eyes may also occur. A positive Babinski

reflex and hemiparesis are usually absent unless brainstem involvement occurs.

Investigations

The investigations include;

Routine tests. Chest X-ray, electrocardiogram, standard liver function tests, plasma electrolytes and blood gases are usually required, particularly in patients who are unconscious. A coagulation profile and complete blood picture for haemoglobin and platelet estimation are also performed in patients in whom a coagulopathy is suspected.

Computed tomography (CT). This is the investigation of choice as it detects all acute haemorrhages of 1.0 cm or more in diameter, intraventricular extension and internal or external hydrocephalus. However, small pontine haemorrhages may not be identified due to motion or posterior fossa bony artifact. After 14 days the haemorrhagic lesion becomes isodense with the surrounding brain.

MRI angiography. This may be used to detect tumor haemorrhage, occult vascular malformations and previous haemorrhages that are poorly detected by CT.

Cerebral angiography. This is not indicated unless an A-V malformation or intraparenchymal extension of a ruptured intracranial saccular aneurysm are suspected.

Lumbar puncture. This carries considerable risk of herniation and in general should not be performed.

Treatment

The principles of therapy to prevent complications are similar to those recommended for acute ischaemic stroke.^{2,3}

Resuscitation and preventative therapy

Management includes respiratory support (e.g. maintaining a clear airway, and preventing aspiration, hypoxia, and hypercapnoea, particularly in patients who are drowsy or unconscious, or have brainstem dysfunction with reduced glottic reflexes and vomiting), cardiovascular support (e.g. systolic or diastolic blood pressure up to 185 mmHg and 110 mmHg, respectively, are tolerated and antihypertensives considered if the mean arterial pressure is consistently > 130 mmHg.⁴), metabolic support (e.g. hydration, electrolyte, acid-base balance) and nutrition are monitored and maintained.

If the patient has a reduced conscious state then standard management of an unconscious or partially conscious patient applies to prevent deep vein thrombosis, pressure sores and contractures. While low-dose unfractionated or low-molecular weight heparin prevents deep vein thrombosis, the risk of fatal pulmonary embolism is lower than the risk of intracranial haemorrhage in these patients.⁵ Therefore,

to decrease the incidence of deep vein thrombosis, routine leg exercises, intermittent pneumatic leg or calf compression,⁶ elastic stockings, physiotherapy and early mobilization should be considered. Pressure sores are reduced by regularly altering the patient's position, supporting the area surrounding pressure points and alternating pressure airflow mattresses,⁷ and physiotherapy with active and passive range movements and splints can prevent contractures.⁸ A urinary catheter will be necessary if the patient is incontinent or unconscious.

Oral anticoagulation associated intracerebral haemorrhage should be immediately reversed using fresh frozen plasma and vitamin K. Hyperthermia should be managed by correcting hydration and active cooling if the temperature exceeds 40°C.⁹ Corticosteroids are of no benefit.¹⁰

Surgery

Surgical treatment with removal of the clot is seldom beneficial, unless the clot is near the surface, the patient is conscious, and there are cerebral CT scan signs of intracerebral shift (i.e. > 5 mm) or compression of vital structures. If surgical removal of the clot is performed, then an intracerebral pressure monitor is usually inserted at the same time to manage episodes of raised intracranial pressure. Stereotactic catheter insertion with aspiration and direct thrombolytic infusions have also been used with variable success in patients with deeper intracerebral haematomata.¹¹⁻¹⁴

With an acute cerebellar haematoma, conservative management may be chosen if the patient has a Glasgow coma score of 13 - 14 and the haematoma is < 3 cm.^{15,16} However, if the haematoma is > 3 cm or if the patient deteriorates (particularly within the first 1 - 2 days) surgical evacuation of the clot with ventricular drainage (if there is an internal hydrocephalus) is the treatment of choice.¹⁷

ACUTE SUBARACHNOID HAEMORRHAGE

Ruptured intracranial saccular (berry) aneurysms are the commonest cause of an acute spontaneous SAH. Other causes include 'angiogram negative' SAH, tumor and AV malformations although typically an AV malformation presents as an intraparenchymal or intraventricular haemorrhage.¹⁸

Intracranial saccular aneurysms are small thin walled pouches that vary from 2 mm to 3 cm in diameter (they are usually > 1 cm when they rupture) and are thought to be the result of developmental defects in the media and elastica of cerebral vessels. The aneurysms often protrude from the arteries, or major branches, of the circle of Willis, and are usually positioned at arterial bifurcations. Approximately 80 - 85% arise from the anterior part of the circle of Willis (e.g. at the junctions

of the anterior communicating artery with the anterior cerebral artery, internal carotid and posterior communicating artery or bifurcation of the middle cerebral artery) and 15 - 20% arise from the vertebrobasilar system (e.g. at the bifurcation of the basilar artery or at the junctions of the basilar artery and superior cerebellar artery or anterior inferior cerebellar artery, or the junction of the vertebral artery and the posterior inferior cerebellar artery. Figure 1). There is more than one aneurysm (usually two or three) in 10 - 20% of patients, and each year new aneurysms develop in at least 2% of patients with previously ruptured aneurysms.¹⁹

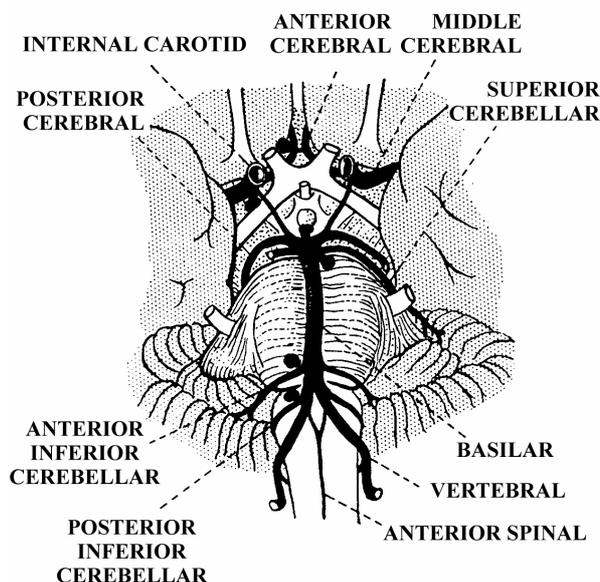


Figure 1. Arterial supply to the brain with cerebral aneurysms shown at their common sites (e.g. at the junctions of the anterior communicating artery with the anterior cerebral artery, internal carotid and posterior communicating artery or at the bifurcation of the basilar artery or at the junctions of the basilar artery and superior cerebellar artery or anterior inferior cerebellar artery, or the junction of the vertebral artery and the posterior inferior cerebellar artery).

A rupture of an intracranial saccular aneurysm is more common in females than males with a peak incidence in the sixth decade. Cigarette smoking, hypertension and high alcohol consumption (usually binge drinking) have been implicated as risk factors. The role of hypertension, however, is somewhat unclear, with some studies concluding that it increases the risk of aneurysmal rupture,^{20,21} and other studies not confirming this.^{22,23} Oral contraceptives (as well as hormonal changes related to menopause and pregnancy) and cocaine have also been implicated.

Patients who have berry aneurysms have a higher incidence of coarctation of the aorta, polycystic disease of the kidney and Marfan's syndrome and a higher

incidence of first and second degree relatives with a confirmed intracranial aneurysm. However, screening for intracranial aneurysms with MRI angiography is usually only performed in familial aneurysm relatives and autosomal dominant polycystic disease patients.¹⁸

Clinical features

Prodrome Before they rupture, the aneurysms may be asymptomatic, although in up to 50% of patients a minor prodromal haemorrhage may present as an instantaneous, generalised and severe headache (i.e. unlike a migraine or tension headache, which are less severe and have a gradual onset).²⁴ The uncharacteristic severity of the headache is often the reason why medical advice is sought. The site of the headache is usually a poor localizing symptom for the aneurysm, with the exception of internal carotid posterior communicating aneurysms, in which the headache is often ipsilateral and retro-orbital.²⁴

Symptoms and signs of motor weakness and speech disturbances (middle cerebral artery aneurysm), nausea and vomiting (anterior communicating artery aneurysm), impaired extraocular muscle function (e.g. a 3rd nerve palsy with a posterior communicating artery aneurysm) as well as neck pain and photophobia may occur at this stage (although neck stiffness may take 6 hours to develop).²⁵ The prodromal episode often precedes the devastating rupture by a few days or weeks and warrants urgent investigation by cerebral CT scan and lumbar puncture.^{24,26}

Rupture. While rupture is characteristically believed to occur when the patient is severely hypertensive (i.e. with strenuous physical activity such as lifting, defaecation, coitus, coughing or parturition), in one study of patients with SAH, 32% occurred with exertion and 36% occurred during sleep.²⁷

The patient presents with sudden and excruciating headache and a brief period of confusion, 12% of these patients lapse into a coma and die, and a further 40% will die within the first two weeks unless treated correctly.²⁸ However, of the patients who present with a symptom of a sudden 'worst headache', if the neurological examination is normal, only 12% will have a SAH and if the neurological examination is abnormal 25% will have a SAH.²⁹

Signs of meningism are found and cerebral posturing may appear in patients who lose consciousness. Subhyaloid haemorrhages may be observed on fundoscopy in 25% of patients, and a third nerve palsy may indicate posterior communicating artery compression of the third nerve. The patients are often clinically graded according to their conscious state (Table 1).³⁰ This scale can also be equated to the patient's Glasgow coma score (Table 2).³¹

Table 1 Hunt and Hess clinical grading of consciousness with ruptured saccular aneurysm

<i>Grade</i>	<i>Signs</i>
I	Fully conscious, no neurological deficits and mild headache
II	Drowsy, no neurological deficits and moderate to severe headache
III	Drowsy and confused, focal neurological deficits
IV	Stupor, moderate or severe neurological deficits
V	Coma, usually moribund with extensor rigidity

Table 2 Glasgow coma score grading of consciousness with ruptured saccular aneurysm

<i>Hunt and Hess grade</i>	<i>Glasgow coma score</i>
I	15
II	12 - 14
III	9 - 11
IV	6 - 8
V	3 - 5

Investigations

The investigations include:

Routine tests. Chest X-ray, electrocardiogram, standard liver function tests, plasma electrolytes, haemoglobin and blood gases are usually required and platelet estimation and a coagulation profile are also performed in patients in whom a coagulopathy is suspected.

Computed tomography (CT). A non-contrast head CT scan is the investigation of choice as it will demonstrate subarachnoid blood in almost 100% of cases if performed within the first 12 hr, and 82% of cases if performed after 12 hr of the SAH (if a contrast CT is performed the arterial enhancement in the basal cisterns may be mistaken for clotted blood).³² Small collections of subarachnoid blood are more likely to be detected if 3.0 mm cuts are taken through the brainstem and parallel to the hard palate, rather than the standard 10 mm cuts.²⁹ The intracerebral damage due to the rupture and the aneurysm may also be demonstrated. Helical CT angiography has also been used to detect an intracranial aneurysm and is useful in detecting new aneurysms in patients in whom MRI angiography is contraindicated (e.g. prior intracranial ferromagnetic clips).

Lumbar puncture. This is performed only if the CT scan fails to demonstrate subarachnoid blood²⁶ (although to allow the development of xanthochromia, it should be delayed until 12 hr after the onset of the headache).²⁵

After the subarachnoid bleed, xantho-chromia (which should be measured by spectro-photometry) will remain for 2 weeks in all patients.³³

Angiography. This is usually performed within the first 3 days and often within 24 hr (i.e. when the patient is haemodynamically stable) to demonstrate the site of the lesion and the presence of multiple aneurysms. A repeat angiogram will detect an aneurysm in approximately 20% of patients who have an 'angiogram negative' SAH.³⁴ While 5 - 10% of patients with SAH will have no aneurysm demonstrated on follow-up angiography, these patients also have a very low rate of rebleeding.³⁵

MRI angiography. This may detect aneurysms of 5 mm or greater, and is often used to screen for intracranial aneurysms (e.g. in patients who have a strong family history of cerebral aneurysm or autosomal dominant polycystic disease patients) or if angiography is contraindicated. It may also detect an intracranial aneurysm with a thrombus in the aneurysmal sac which may not be visualized by angiography.

Complications

Rebleeding. This has a peak incidence at 3 - 10 days following the initial bleed, and occurs in 25% of cases.³⁶ Patients who rebleed have a 40% mortality with the second haemorrhage. In patients who have multiple aneurysms, there is a 1 - 2 % annual risk of rupture of the unruptured aneurysms. The lifetime risk of rupture of these aneurysms has been calculated¹⁸ as 1 - (1-annual risk of rupture)^{expected years of life}.

One study reported that the likelihood of rupture of an intracerebral aneurysm less than 10 mm in diameter in a patient who has not had a previous SAH was extremely low (e.g. 0.05% per year) with surgery having a higher morbidity and mortality than medical treatment.³⁷ This contrasted with patients with previous SAH who had an eleven-fold increased incidence of rupture of a different aneurysm with a diameter < 10 mm (i.e. 0.5% per year), with the annual risk approaching 1% for larger aneurysms (i.e. ≥ 10 mm) and 6% per year for the rare giant (i.e. ≥ 25 mm) aneurysms.³⁷

Cerebral vasospasm. This occurs in 40 - 60% of all patients with SAH. It is due to smooth muscle contraction in cerebral vessels caused by intrathecal oxyhaemoglobin released by red blood cells in close proximity to the vessel.³⁸ It produces a delayed deterioration in conscious state, with an onset of 3 days, a peak incidence at 7 days and resolution 14 days after the SAH. The spasm occurs largely in the cerebral arteries near the source of the haemorrhage,³⁹ and if severe will produce cerebral infarction.

It is detected clinically and usually confirmed by cerebral angiogram, although transcranial Doppler

ultrasound can also be used, which records high velocities when vasospasm is present.⁴⁰ A brain CT scan can also be performed to detect the adverse effects of vasospasm (e.g. ischaemia, infarction).

Acute hydrocephalus. This occurs in 30% of patients with an acute SAH,⁴¹ being particularly common with aneurysms of the anterior communicating artery. It usually presents as an increased impairment of consciousness and is caused by blood obstructing the arachnoid villi (external or communicating hydrocephalus) or clot obstructing the lateral ventricles, aqueduct of Sylvius or the foramen of Magendie and Luschka (internal or non-communicating hydrocephalus). The initial management is to wait for spontaneous improvement or to perform a lumbar puncture (or serial lumbar punctures) if no intracerebral haematoma or intraventricular blood is detected by CT scan.⁴² Approximately 7% of patients require surgical treatment with ventricular drainage.^{41,43}

Seizures. These are uncommon but may occur in up to 10% of patients at the time of haemorrhage.⁴⁴

Neurogenic pulmonary oedema. This is probably caused by a sympathetic discharge associated with the SAH leading to high vascular pressures in both the systemic and the pulmonary circulation. Fluid with a high protein content is sequestered into the pulmonary interstitium and alveolar spaces due to the dramatic, but often transient, pulmonary capillary hypertension.⁴⁵⁻⁴⁷ Treatment is the same as for the adult respiratory distress syndrome.

Cardiovascular abnormalities. Approximately 25% of patients with SAH have ECG abnormalities consistent with myocardial ischaemia or myocardial infarction. These include cardiac arrhythmias (e.g. supraventricular and ventricular tachycardias, ventricular fibrillation and heart block), and ECG abnormalities of T wave changes (e.g. peaked, flattened or deeply inverted T waves), prominent U waves, QT prolongation, depressed ST segments, elevated ST segments, and even transient Q waves.⁴⁸ These usually

occur immediately on cerebral insult, last for as long as 11 days, and are thought to be due to hypothalamic stimulation causing an imbalance in autonomic outflow leading to either an increase in local release of norepinephrine or intravascular release of autonomic mediators.⁴⁸ Prolonged sympathetic stimulation has been associated experimentally with subendocardial ischaemia, and corresponding transient regional wall abnormalities have been demonstrated by echocardiography.⁴⁹ Reversible cardiogenic shock has also been reported.⁵⁰

One study found that the ECG changes of myocardial ischaemia and infarction associated with SAH were associated with a more severe neurological

injury but did not independently predict an increased risk of death (i.e. were not associated with an increased risk of death from cardiac causes).⁵¹

Cerebral oedema. Generalised cerebral oedema is rare and usually indicates a severe and lethal haemorrhage.

Acute gastric erosions. Clinically important bleeding occurs in up to 6% of patients with acute SAH,⁵² even if early enteral nutrition is tolerated (serum glucose ideally should be kept below 10 mmol/L). Therefore, H₂ blockers (ranitidine 50 mg i.v. 8-hourly) or proton-pump inhibitors (omeprazole 40 mg i.v. daily) should be given prophylactically.

Hyponatraemia. This may be caused by cerebral salt wasting or a syndrome of inappropriate antidiuretic hormone secretion (SIADH) usually caused by excessive antidiuretic hormone secretion in the presence of excessive intravenous or ingested water.

The underlying cause for cerebral salt wasting syndrome in SAH is not clear,^{53,54} although increased secretion of brain natriuretic hormone and suppression of aldosterone synthesis have been recorded.⁵⁵ The cerebral salt wasting syndrome is usually associated with hypovolaemia and an elevated plasma urea, whereas SIADH is associated with hypervolaemia and a low plasma urea. Management of the cerebral salt wasting syndrome requires i.v. 0.9% saline 2 - 6 L/day and fludrocortisone 0.2 mg 12-hourly.⁵⁶ Management of SIADH requires water restriction and, rarely, hypertonic saline.

Treatment

Resuscitation and preventative therapy

The principles of resuscitation and therapy to prevent complications are similar to those recommended for acute intracranial haemorrhage. Management of the headache requires paracetamol although i.v. morphine 1-2 mg is also often required.⁵⁷ While antiseizure prophylaxis is used in some centers prior to surgery, the practice has not been shown to be of benefit.⁵⁷ Phenytoin (20 mg/kg i.v. over 20 minutes) is used if seizures occur.

Antihypertensive agents

These are often used to control the blood pressure in an attempt to reduce rebleeding, so that the systolic blood pressure is kept less than 140 mmHg,⁵⁸ or the mean arterial pressure (MAP) is kept at no greater than 90 mmHg (e.g. using i.v. esmolol 1.75 mg/70 kg/min and sodium nitroprusside 15 - 100 µg/min initially, then subsequently oral metoprolol 100 - 200 mg daily and captopril 25 - 150 mg daily). One study reported that

keeping the MAP below 125 mmHg during the first 6 hours after presentation was all that was required to half the mortality rate associated with SAH.⁵⁹

As cerebral vasospasm is exacerbated by hypotension, surgery should be performed early (to reduce the incidence of rebleeding) and thereafter a MAP of at least 100 mmHg (and even up to 130 mmHg⁵⁷) should be achieved.

Surgery

Clipping the aneurysm is the preferred treatment, and with experienced operators the mortality for a grade I - III patient should be less than 5%. Surgery for grade I - III patients (i.e. good-risk patients) is performed early (i.e. within the first 3 days⁶⁰⁻⁶³ and often within 24 hr). Ventricular drainage may be performed at the same time to monitor and manage internal or external hydrocephalus as the incidence of rebleeding is increased if ventricular drainage is performed before clipping of the aneurysm.¹⁸ Some have also advocated early clipping and evacuation of intracerebral haematoma in moribund patients (i.e. grade V).⁶⁴

Postoperative antibiotic prophylaxis is often prescribed using a cephalosporin with activity against *Staphylococcus aureus* (e.g. cephazolin 1 gm 8-hourly for 1-3 days).

Endovascular therapy

Intravascular techniques with Guglielmi detachable coil embolisation have been used successfully in selected patients in whom surgical clipping is not medically or technically feasible.¹⁹ While complications of endovascular occlusion include incomplete aneurysm obliteration, aneurysm regrowth or perforation and thromboembolic events, improvements in coil technology, aneurysm localisation and operator technique are allowing more patients to be considered for this form of therapy.^{65,66}

Fibrinolytic agents

Fibrinolytic agents have been used in patients with cerebral haemorrhage after surgery. In six patients, intraventricular haemorrhage was treated with urokinase 10,000 U into the lateral ventricle followed by 1 hr of drain clamping once or twice daily for 1 to 10 days. No rebleeding occurred and, on average, both the third and fourth ventricles became clear on the third day following treatment.⁶⁷ In a case report, intraventricular alteplase (8 mg daily for two days) was used successfully to lyse an intraventricular haematoma which developed following the clipping of a cerebral aneurysm.⁶⁸

In a meta-analysis of patients with intraventricular haemorrhage caused by extension from SAH or intracerebral haemorrhage, treatment with ventricular drainage combined with fibrinolytic agents was associated with an improved outcome.⁶⁹

Antifibrinolytic agents

While antifibrinolytics may lower the rebleeding rate, they increase the rate of hydrocephalus and ischaemic deficits, and have no effect on mortality associated with ruptured saccular aneurysms.^{70,71} Therefore, until methods are found to limit ischaemic complications, antifibrinolytic agents should not be used to treat ruptured saccular aneurysms.^{70,71}

Treatment of vasospasm***Prophylactic calcium antagonist therapy***

1. *Nimodipine*. The calcium-channel blocker nimodipine if administered within the first 3 days of the SAH at 0.25 µg/kg/min (i.e. 1 mg/hr/70 kg) for 2 hr, increasing to 0.5 µg/kg/min (i.e. 2 mg/hr/70 kg) for 7 - 10 days, and thereafter orally (60 mg 4-hourly) for 21 days, or at least for 5 days after clipping the aneurysm, reduces the delayed ischaemic deficit and improves the outcome in patients with aneurysmal SAH.⁷²⁻⁷⁶ The reason for the protective effect of nimodipine is unknown, and may not be related to relaxation of the cerebral vessels (as it does not affect the severity of angiographically observed vasospasm⁷⁷) but due to a protective effect on neurones due to a reduction in the intracellular calcium level.⁷⁸

2. *AT877*. The calcium antagonist AT877, unlike nimodipine, inhibits the action of free intracellular calcium. An intravenous dose of 30 mg over 30 min 8-hourly for 14 days following surgery has been reported to significantly reduce the incidence of symptomatic vasospasm, comparable to that of nimodipine, with a reduction in angiographically demonstrable vasospasm,⁷⁷ although, evidence that it reduces morbidity and mortality is inconclusive.⁷⁹

3. *Tirilazad mesylate*. The 21-aminosteroid, tirilazad mesylate, reduces cerebral vasospasm in experimental animals. In a large randomised, double-blind controlled trial of patients with aneurysmal SAH, intravenous nimodipine and tirilazad mesylate (6 mg/kg daily for 10 days) was associated with a reduction in mortality and morbidity at 3 months.⁸⁰ As the beneficial effect was greater in males than females, another study of female patients with SAH using a larger dose of tirilazad mesylate (15 mg/kg/day) found a significant reduction in the incidence of symptomatic vasospasm in the treatment group but no change in the mortality rate at 3 months.⁸¹

Haemodynamic support

Initial management of patients with vasospasm often uses methods to increase cardiac output and blood pressure in an attempt to increase cerebral perfusion and

promote cerebral blood flow³⁹ (i.e. 'triple H' therapy of hypertension, hypervolaemia and haemodilution),⁸² and in such circumstances an arterial cannula and right heart catheter should be inserted to closely monitor the intravascular pressures. However, no prospective randomised controlled trials have yet been performed confirming the efficacy of 'triple H' therapy,⁶⁰ and haemorrhagic infarction and cerebral oedema may even be exacerbated if hypervolaemic therapy is used.⁸³ Normovolaemia, normal blood pressure (for that patient), and normal haemoglobin levels may be just as beneficial.

Angioplasty

Vasospasm unresponsive to hypervolaemic and hypertensive therapy has also been treated by intraarterial papaverine (5 mg/minute for 45 minutes if the vasospasm is diffuse⁸⁴) or balloon angioplasty for focal vasospasm.^{85,86} In one study, angioplasty followed by a selective intra-arterial papaverine infusion (1 mL of 0.2% papaverine over 10 seconds) into the cerebral artery just proximal to the site not accessible to the angioplasty balloon reversed angiographically confirmed vasospasm.⁸⁷ However, there have been no prospective, randomised studies to confirm the beneficial effects on mortality of intraarterial papaverine⁸⁸ or balloon angioplasty.⁸⁹

Thiopentone

In one study of 11 patients who developed papaverine and balloon angioplasty resistant vasospasm following surgical treatment of aneurysmal SAH, thiopentone (10 mg/kg over 20 minutes and continued at an average of approximately 500 mg/hr for up to 3 days) was associated with an improved outcome when compared with historical controls.⁹⁰

Nimodipine

While some report that treatment with nimodipine once cerebral vasospasm is established has no effect⁹¹ others have reported a beneficial effect.⁹²

Magnesium sulphate

Intravenous and intrathecal magnesium sulphate have been used to successfully reverse experimental cerebral vasospasm.⁹³ However, human studies have not yet been performed to confirm these results.

Endothelin receptor inhibitors

These have been shown to prevent and reduce cerebral vasospasm occurring after experimental SAH.^{94,95} However, large clinical studies have not yet been performed.

Other vasodilators

Ketanserin, phenoxybenzamine, phentolamine, chlorpheniramine, propranolol, salbutamol, theophylline, superoxide dismutase, atropine and methysergide have all consistently failed to reverse cerebral vasospasm.³⁸

Intrathecal alteplase

In a primate model of SAH and vasospasm, treatment with intrathecal alteplase prevented vasospasm.⁹⁶ In 40 patients who underwent surgical clipping of a ruptured aneurysm within 72 hr of the SAH, postoperative intrathecal alteplase (i.e. 3, 5, 10 or 13 mg, administered at the end of the operation) or 0.5 mg 8-hourly for three doses, reduced the incidence of vasospasm.^{97,98} In another study of 105 patients who underwent surgery within 48 hr of the SAH, intrathecal alteplase 2 mg on the day after surgery and daily for 5 days (to a total of 10 mg), reduced the incidence of vasospasm.⁹⁹ While a randomised study of 100 patients undergoing aneurysmal surgery for SAH found no significant benefit with the interoperative use of 10 mg of intracisternal alteplase, a significant reduction in severe vasospasm was noticed in patients who had thick subarachnoid clots.¹⁰⁰

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