**Review Article** 

egneuro,01(02):21-28,2019

# **Anaesthetic Management of Cerebral Aneurysm Surgery**

### Raju Shrestha<sup>1</sup>

<sup>1</sup>Department of Anesthesiology, B & C Medical College and Teaching Hospital & Research Center,Birtamode,Jhapa,Nepal

### **Correspondence:**

Dr Raju Shrestha

Department of Anesthesiology, B & C Medical College and Teaching Hospital & Research Center,Birtamode,Jhapa,Nepal. Email: *rajustha6022@gmail.com* Phone: +9779851164710

Management of cerebral aneurysm is always a challenge for a neurosurgeon and anaesthesiologist. Proper knowledge, experience, timely intervention and goal directed therapy will definitely save a lot of lives. The leading causes of death and disability were, in descending order, vasospasm, the direct effects of the initial bleed (massive subarachnoid, subdural, or intracerebral hematoma, permanent ischemic effects of increased intracranial pressure, rebleeding, and surgical complications. This article revises the anaesthetic challenges during managing the cerebral aneusysms.

Key words: aneurysm, anesthesia, intraoperative challenge

anagement of cerebral aneurysm is always а challenge for а neurosurgeon and anaesthesiologist. Proper knowledge, experience, timely intervention and goal directed therapy will definitely save a lot of lives. The leading causes of death and disability were, in descending order, vasospasm, the direct effects of the initial bleed (massive subarachnoid, subdural. intracerebral hematoma. or permanent ischemic effects of increased intracranial pressure [ICP]), rebleeding, and surgical complications.<sup>1</sup>Successful anesthetic management of patients with cerebral aneurysms requires a thorough understanding of the natural history, pathophysiology, and surgical requirements of the procedures.

Preoperative considerations: 21 Date Submitted: 29/8/2019 Date Accepted: 11/9/2019 The main steps in preoperative evaluation are as follows:

1. Assessment of the patient's neurologic condition and clinical grading of the subarachnoid hemorrhage (SAH)

2. A review of the patient's intracranial pathologic condition, including the performing of computed tomography (CT) and angiograms

3. Monitoring of ICP and transcranial Doppler ultrasonography (TCD) if available

4. Evaluation of other systemic functions, premorbid as well as current condition, with emphasis on systems affected by SAH

5. Communication with the neurosurgeon regarding positioning, anticipated difficulty/technique to clip and special monitoring requirements

6. Optimization of the patient's condition by correcting any existing biochemical and physiologic disturbances.

The preoperative assessment allows appropriate planning of an anesthetic regimen with consideration of the pathophysiology of all organ systems as well as the surgical and monitoring requirements. This approach facilitates the goals of smooth anesthesia for an uncomplicated aneurysm and ensures a heightened level of preparedness for a complicated one.<sup>2</sup>

Although the surgical mortality and morbidity vary with different institutions, patients in good preoperative condition (assigned to clinical grades I and II) can be expected to do well; patients with grade V status have a high mortality and morbidity, but aggressive management has resulted in substantial improvement (Table 1).<sup>3</sup>The clinical grade also indicates the severity of associated cerebral pathophysiology. The higher the clinical grade, the more likely the occurrence of vasospasm, elevated ICP<sup>4,5</sup>impairment of cerebral auto- regulation<sup>6,7</sup> and a disordered cerebrovascular response to hypocapnia.<sup>5</sup> A worse clinical grade is also associated with a higher incidence of cardiac arrhythmia and myocardial dysfunction.8,9

Patients with worse clinical grades have a tendency to become hypovolemic and hyponatremic.<sup>10,11</sup>Thus, understanding the grading scale allows the anesthesiologist to communicate effectively with other physicians and facilitates assessment of pathophysiologic derangements and the planning of perioperative anesthetic management.

Table1:	Mod	lified Hu	nt and	Hess Clinical	
Grades	for	Patients	with	Subarachnoid	
Homonuhaga*					

Hemorrhage*		
Grades	Criteria	
0	Unruptured aneurysm	
Ι	Asymptomatic or minimal headache and slight nuchal rigidity	
II	Moderate to severe headache, nuchal rigidity, but no neurological deficit other than cranial nerve palsy	
III	Drowsiness, confusion, or mild focal deficit	
IV	Stupor, mild or severe hemiparesis, possible early decerebrate rigidity, vegetative disturbance	
V	Deep coma, decerebrate rigidity, moribund appearance	

\*Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography result in assignment of the patient to the next less favorable category.

Table 2	Surgical	Mortality	and	Major	
morbidity	of Sub	arachnoid	hemo	orrhage	
according to Clinical Grades					

Grade	Mortality	Morbidity
(Hunt and	(%)	(%)
Hess)		
0	0-2	0-2
Ι	2-5	0-2
II	5-10	7
III	5-10	25
IV	20-30	25
V	30-40	35-40

**Intraoperative considerations:** 

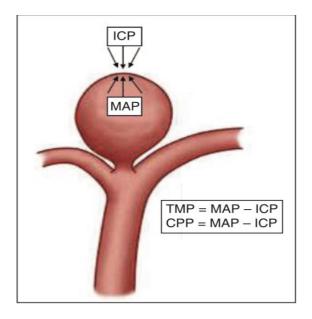


Figure 1 Transmural pressure = Mean arterial blood pressure (MAP) — intracranial pressure (ICP); cerebral perfusion pressure = MAP — ICP

Any sudden rise in blood pressure during tracheal intubation can result in rupture of aneurysm. Therefore, the goal during induction of anesthesia is to reduce the risk of aneurysm rupture by minimizing the transmural pressure (TMP) while simultaneously maintaining an adequate cerebral perfusion pressure (CPP). As illustrated in Figure 1, both TMP and CPP are determined by the same equation, mean arterial blood pressure (MAP) minus ICP (MAP — ICP). Thus these goals represent opposite objectives.<sup>12</sup>

Blood pressure management should be done taking into account patient's clinical grade and baseline blood pressure values. Patients who have been normotensive or those with SAH Grades 0, I, and II generally have normal ICP and are not experiencing acute ischemia.<sup>13</sup>These patients, therefore, tolerate a bigger transient decrease in blood pressure (30-

egneuro Volume 01, 2019

35%). In contrast, patients with poor clinical grades frequently have increased ICP, low CPP, and ischemia.<sup>14</sup>The elevated ICP decreases the TMP and partially protects the aneurysm from re-rupture. These patients may not tolerate transient hypotension as well, and the duration and magnitude of blood pressure decrease should be moderated. As a general principle, the patient's blood pressure should be reduced to 20-25% below the baseline value, prophylaxis and to blunt the hypertensive response to laryngoscopy and intubation should be instituted before tracheal intubation is attempted.

Similarly, discretion should be used whether hyperventilation will be beneficial or harmful. Patients with a good clinical grade should not be hyperventilated, because the reduction in CBF will lead to a reduction in ICP and consequently, an increase in TMP. Conversely, patients with poor clinical grades should be managed with moderate hyperventilation to improve cerebral perfusion. Sudden changes in MAP should be avoided to reduce the risk of aneurysm rupture and ischemia.<sup>15</sup>

#### Monitoring

Standard monitoring usually includes 5-lead electrocardiogram, continuous intra-arterial pressure, pulse oximetry, capnography, urinary output, body temperature, and neuromuscular block. It is preferable to initiate invasive blood pressure monitoring prior to induction. Many neuroanesthetists routinely insert a central venous catheter for guidance of intravascular the injection volume. for of potent cardiovascular drugs in the case of severe cardiovascular instability. and for the administration of mannitol (which may cause local inflammation when administered through a smaller peripheral vein.<sup>16</sup>

### Neurophysiologic monitoring

Although no randomized controlled trials have documented improved outcomes with neurophysiologic monitoring for surgical aneurysm clipping, it is widely used in many institutions. Most commonly used modalities electroencephalography and are evoked potentials (somatosensory evoked potentials, motor evoked potentials, brainstem auditory evoked potentials).<sup>17</sup>, <sup>18</sup>Anesthetic agents should be selected to facilitate reliable recordings. One of the key elements is to keep anesthetic depth stable. Volatile anesthetics should remain below 0.5 minimum alveolar concentration when somatosensory evoked potentials and motor evoked potentials are recorded. Muscle relaxants should be avoided after induction when motor evoked potentials are monitored. However, it is mandatory to maintain adequate anesthetic depth to insure immobility. A propofol and opioid infusion should be titrated appropriately. Change in neurophysiologic recordings should prompt the surgical team to re-evaluate clip placement and the anesthesiologist to ensure that blood pressure, pharmacology and oxygenation are optimal.

### Maintenance of anesthesia

The goals during maintenance of anesthesia are to:  $^{19}$ 

- 1. Provide a relaxed or "slack" brain that will allow minimal retraction pressure.
- 2. Maintain perfusion to the brain.
- 3. Reduce TMP if necessary during dissection of the aneurysm and final clipping and
- 4. Allow prompt awakening and assessment of patients with good SAH grades.

The choice of anesthetic agents should take into account the brain condition based on 24

preoperative radiologic investigations and Hunt and Hess grading. Either an I.V. or inhalation anesthetic or a combination of both can be used to provide such conditions. Propofol has cerebral vasoconstrictive actions, thus it causes decrease in CBF, cerebral metabolic rate and thus decreases ICP.<sup>20,21</sup>Isoflurane, sevoflurane and desflurane may also be used in concentrations <1 minimum alveolar concentration (MAC) beyond which these cause increase in ICP.

Intraoperative analgesia is provided either by intermittent boluses or infusions of opioids. Periods of intense stimulation like pin insertion, skin incision or elevation of periosteum and incision of duramater should be covered by administering additional doses of opioids and deepening the planes of anesthesia to prevent hypertension.<sup>19</sup>

# **Brain relaxation**

Optimal brain relaxation and reduction in brain bulk helps surgical exposure, reduce the forces required for brain retraction, and facilitates clipping of the aneurysm. Following agents/maneuvers have been used in combination:<sup>22,23</sup>

1. Positioning

15-30° head up position is the optimal position which decreases ICP yet maintains CPP. Excessive neck flexion or rotation should be avoided. Endotracheal tube should be taped instead of tying it around the neck. If it has to be tied across the neck, it should be ensured that the tie is not too tight and there is no pressure on neck veins.

2. Mannitol

Mannitol is usually the drug of choice to decrease brain water content. 20% mannitol (0.5-2 g/kg) is usually given over 30 min. The usual dose is 1 g/kg; an additional dose is given when indicated by the brain conditions. A total dose of 2 g/kg is frequently given when temporary artery occlusion is planned.

3. Frusemide

Frusemide reduces CSF formation and water and ion movement across the blood-brain barrier. The prolonged diuresis after the administration of frusemide can potentiate the effect of mannitol by sustaining elevated serum osmolality.<sup>24</sup> Frusemide is used in a dose of 0.25-1 g/kg.

4. Hypertonic saline

Hypertonic saline (3%) is a equiefficacious to 20% mannitol in the extent of brain relaxation.<sup>25</sup> However, mannitol continues to remains the drug of choice for intraoperative brain relaxation.

5. Cerebrospinal fluid drainage

Decreasing the volume of CSF using a lumbar subarachnoid or ventriculostomy catheter is an effective means of reducing brain bulk and may become necessary to achieve satisfactory brain relaxation. Extreme caution should however, be exercised during insertion of the drain to minimize CSF loss and a sudden decrease in ICP, so as to avoid an abrupt increase in TMP and a re-bleed. Due to the risk of brainstem herniation, lumbar drainage of CSF is contraindicated in patients with intracerebral hematoma. In theory, free drainage should be allowed only after the dura is open to minimize the risk of rebleeding; in practice; however, 20-30 mL of CSF is usually drained just before dural opening to facilitate dural incision. The drain is usually left open

during the procedure, until the aneurysm is clipped or until the beginning of dural closure.

6. Hyperventilation

Controlling  $CO_2$ levels can be used therapeutically to lower ICP. However, excessive hyperventilation carries the risk of inducing ischemia especially in poor grade patients. Thus, use of hyperventilation should be individualized according to the operating conditions. A reasonable approach is to institute mild hypocapnia (30-35 mm Hg) before the dura is open, moderate hypocapnia (25-30 mm Hg) after the dura is open, and normocapnia relative during induced hypotension and after the aneurysm is clipped.<sup>19</sup>

Fluid and Electrolyte Balance

Fluid should be administered according to the patient's need and guided by intraoperative blood loss, urine output, and CVP, if present, or other dynamic index of volume status such as pulse pressure variation.<sup>26</sup>Intravenous fluid should not be withheld if induced hypotension is planned, because hypovolemic hypotension is detrimental to organ perfusion. The aim is to normovolemia before aneurysm maintain clipping and slight hypervolemia after clipping. Electrolytes should be replaced as needed. Glucose-containing solutions should not be given, because evidence exists that hyperglycemia may aggravate both focal and global transient cerebral ischemia.<sup>27,28</sup>Because lactated Ringer's solution is relatively hypo-osmolar, a more physiologic solution, such as PlasmaLvte. Normosol, or normal saline, is preferred. Some practitioners use 5% albumin after clipping of the aneurysm, but the advantages of this protocol have not been documented. On the

other hand, hetastarch probably should not be used or should be used sparingly (less than 500 mL) because of the risk of intracranial bleeding.<sup>29,30</sup>

Temporary arterial occlusion and brain protection

For large aneurysms and those deemed at risk of intraoperative rupture, surgeons may use temporary occlusion of the proximal artery to facilitate dissection and clipping. To minimize the risk of focal brain ischemia, the period of occlusion should be minimized by a skilled surgeon. A 10min occlusion seems to be safe while more than 20min of occlusion is associated with poor outcomes.31-33Blood pressure should be kept in the high normal with pressors (phenylephrine range or norepinephrine) to maximize collateral flow. Although many surgeons still request some type of pharmacologic brain protection e.g. thiopental or propofol, there are no human studies demonstrating а benefit in neurosurgery.<sup>34,35</sup>There is no convincing evidence for benefit of mild intraoperative hypothermia, but no clear evidence either for harm.<sup>36,37</sup>Hyperthermia and hyperglycemia should be avoided.

Intraoperative aneurysm rupture

Intraoperative aneurysm rupture carries a high morbidity and mortality. It may occur at any time during the procedure, associated mostly with an abrupt increase in the TMPG of the aneurysm (as a consequence of either a sudden increase in blood pressure or an abrupt decrease in ICP) or with surgical manipulation. It is to be expected that rupture of an aneurysm with an open skull and dura carries a better prognosis than a rupture occurring during induction of anaesthesia.

The incidence of aneurysm rupture varies with size and location of the aneurysm, and with surgical experience. Frank intraoperative rupture occurred in approximately 11% of patients with previously ruptured aneurysm (compared with an incidence of 1.2% in previously unruptured aneurysms).<sup>38</sup>Hemorrhagic shock may develop in 8% of aneurysm ruptures.<sup>39</sup>

The choice of acute interventions will depend on the size of the leak/rupture, the completeness of the dissection of the aneurysm and thus the surgeon's direct access to it, and the feasibility of temporary occlusion of blood vessels proximally and distally to the aneurysm. The primary hemodynamic goal during rupture of an aneurysm is maintenance of normovolaemia. Temporary occlusion of cerebral arteries proximal and distal to the aneurysm is an effective means of gaining control over ruptured aneurysms.

The blood pressure management during rupture of an aneurysm is controversial. On the one hand, a transient decrease in MAP to 40-50 mm Hg decreases wall shear stress, reduces bleeding, and facilitates surgical orientation, exposure, and clipping. On the other hand, in the presence of clinically relevant blood loss, the combination of hypotension and hypovolemia may result in profound cerebral ischaemia. Thus, temporary vessel occlusion is the preferred technique to gain control over a aneurysm-with ruptured the possible exception of when temporary occlusion is not possible.40

# Postoperative considerations

Consideration of risk factors, continued treatment for stroke-related conditions, and behavior modification are all necessary in the postoperative period and beyond for prevention of recurrence. In the immediate postoperative period, cerebrovascular imaging may be necessary to identify any remnants or further occurrence of aneurysm. Initiation or continued use of nimodipine for blood pressure control and maintenance of normovolemia is recommended to help prevent Delayed cerebral ischemia.<sup>41,42</sup>

### Conclusion

Anesthetic management of cerebral aneurysm surgery patients is a complex team approach. Careful consideration of individual patient status, techniques, and the safest evidencebased methods are required for successful management

### **Refrences:**

- Kassell NF, Torner JC, Haley Jr EC, et al. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg. 1990;73:18–36.
- 2. Cottrell and Patels Neuroanesthesia 6e Edition
- 3. Le Roux PD, Elliott JP, Newell DW,etal. Predicting outcome in poor-grade patients with subarachnoid hemorrhage: A retrospective review of 159 aggressively managed cases [see comments]. J Neurosurg. 1996;85:39–49.
- Voldby B, Enevoldsen EM. Intracranial pressure changes following aneurysm rupture. Part 1: Clinical and angiographic correlations. J Neurosurg. 1982;56:186–196.
- Heuer GG, Smith MJ, Elliott JP, et al. Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg. 2004;101:408–416.
- Dernbach PD, Little JR, Jones SC, Ebrahim ZY. Altered cerebral autoregulation and CO<sub>2</sub> reactivity after aneurysmal subarachnoid hemorrhage. Neurosurgery. 1988;22:822–826.
- Tenjin H, Hirakawa K, Mizukawa N, et al. Dysautoregulation in patients with ruptured aneurysms: Cerebral blood flow measurements obtained during surgery by a temperaturecontrolled thermoelectrical method. Neurosurgery. 1988;23:705–709.
- 8. Davies KR, Gelb AW, Manninen PH, et al. Cardiac function in aneurysmal subarachnoid haemorrhage:

### egneuro Volume 01, 2019

A study of electrocardiographic and echocardiographic abnormalities. Br J Anaesth. 1991;67:58–63.

- 9. Kothavale A, Banki NM, Kopelnik A, et al. Predictors of left ventricular regional wall motion abnormalities after subarachnoid hemorrhage. Neurocrit Care. 2006;4:199–205.
- Diringer MN, Lim JS, Kirsch JR, Hanley DF. Suprasellar and intra- ventricular blood predict elevated plasma atrial natriuretic factor in subarachnoid hemorrhage. Stroke. 1991;22:577–581.
- 11. Nelson RJ, Roberts J, Rubin C, et al. Association of hypovolemia after subarachnoid hemorrhage with computed tomographic scan evidence of raised intracranial pressure. Neurosurgery. 1991;29:178–182.
- 12. Dorairaj IL, Hancock SM. Anaesthesia for interventional neuroradiology. Contin Educ Anaesth Crit Care Pain 2008;8:86-9.
- 13. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: An updated systematic review of epidemiological studies. Stroke 2005;36:2773-80.
- 14. Priebe HJ. Aneurysmal subarachnoid haemorrhage and the anaesthetist. Br J Anaesth 2007;99:102-18.
- 15. Torre-Healy A, Marko NF, Weil RJ. Hyperosmolar therapy for intracranial hypertension. Neurocrit Care 2012;17:117-30.
- 16. Gruber A, Dorfer C, Standhardt H, Bavinzski G, Knosp E. Prospective comparison of intraoperative vascular monitoring technologies during cerebral aneurysm surgery. Neurosurgery 2011;68:657-73.
- 17. Priebe HJ. Aneurysmal subarachnoid haemorrhage and the anaesthetist. BJA. 2007;99:102–18.
- Drummond JC, Patel PM. Neurosurgical anesthesia. In: Miller RD, editor. Anesthesia. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010. p. 2045–87.
- Dorairaj IL, Hancock SM. Anaesthesia for interventional neuroradiology. Contin Educ Anaesth Crit Care Pain 2008;8:86-9.
- 20. Torre-Healy A, Marko NF, Weil RJ. Hyperosmolar therapy for intracranial hypertension. Neurocrit Care 2012;17:117-30.
- 21. Miura Y, Kamiya K, Kanazawa K, Okada M, Nakane M, Kumasaka A, et al. Superior recovery profiles of propofol-based regimen as compared to isoflurane-based regimen in patients undergoing craniotomy for primary brain tumor excision: A retrospective study. J Anesth 2012;26:721-7.
- 22. Dinsmore J. Anaesthesia for elective neurosurgery. Br J Anaesth 2007;99:68-74.
- Todd MM, Cutkomp J, Brian JE. Influence of mannitol and furosemide, alone and in combination, on brain water content after fluid

percussion injury. Anesthesiology 2006; 105:1176-81.

- Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology 2007;107:697-704.
- ChoiJ,KimTS,JooSP,LeeJK,KimJH,KimSH.Effect oftemporary clipping on the cerebral infarction in middle cerebral artery aneurysm surgery. Korean J Cerebrovasc Surg 2006;8:248-53.
- 26. Qiao H, Zhang J, Liang WM. Validity of pulse pressure and systolic blood pressure variation data obtained from a Datex Ohmeda S/5 monitor for predicting fluid responsiveness during surgery. J Neurosurg Anesthesiol. 2010;22(4):316–322.
- 27. Lanier WL, Stangland KJ, Scheithauer BW, et al. The effects of dex- trose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. Anesthesiology. 1987;66:39–48.
- Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. J Neurosurg. 1991;75:545–551.
- 29. Cully MD, Larson Jr CP, Silverberg GD. Hetastarch coagulopathy in a neurosurgical patient. Anesthesiology. 1987;66:706–707.
- Damon L, Adams M, Stricker RB, Ries C. Intracranial bleed- ing during treatment with hydroxyethyl starch. N Engl J Med. 1987;317:964– 965.
- 31. Samson D, Batjer HH, Bowman G, Mootz L, Krippner WJ Jr, Meyer YJ, et al. A clinical study of the parameters and effects of temporary arterial occlusion in the management of intracranial aneurysms. Neurosurgery. 1994;34:22–9.
- 32. Lavine AD, Masri LS, Levy ML, Giannotta SL. Temporary occlusion of the middle cerebral artery in intracranial aneurysm surgery: time limitation and advantage of brain protection. J Neurosurg. 1997;87:817–24.
- 33. Ogilvy CS, Carter BS, Kaplan S, Rich C, Crowell R. Temporary vessel occlusion for aneurysm surgery: risk factors for stroke in patients protected by induced hypothermia and hypertension and intravenous mannitol administration. J Neurosurg. 1996;84:785–91.
- 34. Hindman BJ, Bayman EO, Pfisterer WK, Torner JC, Todd MM, IHAST Investigators. No association between intraoperative hypothermia or supplemental protective drug and neurologic outcomes in patients undergoing temporary clipping during cerebral aneurysm surgery: findings from the Intraoperative Hypothermia for

Aneurysm Surgery Trial. Anesthesiology. 2010;112:86–101.

- 35. Bilotta F, Gelb AW, Stazi E, Titi L, Paoloni FP, Rosa G. Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials. Br J Anaesth. 2013;110 Suppl. 1:i113–20.
- Todd MM, Hindman B, Clarke WR, Torner JC, for the IHAST Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med. 2005;352: 135–45.
- 37. Li LR, You C, Chaudhary B. Intraoperative mild hypothermia for postoperative neurological deficits in intracranial aneurysm patients. Cochrane Database Syst Rev. 2012. Feb 15;2:CD008445,
- H.-J. Priebe Aneurysmal subarachnoid haemorrhage and the anaesthetist Br J Anaesth 2007; 99: 102–18
- Kassell NF, Torner JC, Haley EC, et al. The international cooperative study on the timing of aneurysm surgery. I. Overall management results. J Neurosurg 1990; 73: 18 – 36
- 40. Leipzig TJ, Morgan J, Horner TG, Payner T, Redelman K, Johnson CS. Analysis of intraoperative rupture in the surgical treatment of 1964 saccular aneurysms. Neurosurgery 2005; 56: 455–68
- 41. Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD000277.
- 42. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm—a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983 Mar 17;308(11):619-624.