Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid hemorrhage: British aneurysm nimodipine trial

BMJ 1989 March 11; 298: 636-642

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening insult to the brain requiring aggressive medical and surgical management. There have been tremendous neurosurgical advancements in securing a ruptured cerebral aneurysm, either with open neurosurgical clipping or neuroendovascular coiling. These techniques have considerably reduced the risks of operation to secure the aneurysm. However even with these advances, the mortality and morbidity from aSAH is still very high. In the past, this was mainly due to a lack of effective medical management for these patients. Specifically, delayed cerebral ischemic or infarction, vasospasm, and re-bleeds are some of the many severe complications from aSAH that are difficult to treat and that are poor prognostic factors. aSAH provides an opportunity for pretreating cerebral ischemia and the calcium channel antagonist nimodipine has been hailed as a neuroprotectant in the literature to reduce the incidence of delayed cerebral ischemia after aSAH. Nimodipine is a cerebral vasodilator that works by blocking voltage gated L-type calcium channels. At the time of this trial, the drug did not appear to reduce the incidence or severity of vasospasm detected by angiography in humans or apes, but it was proven to reduce the size of cerebral infarcts in rats when given before (but not after) occlusion of a cerebral artery. As such, the goal of this study was to determine if Nimodipine could reduce the incidence of both ischemic events and proved cerebral infarction on outcome after aSAH.

Experimental design and statistics:

Design: Double blind, placebo controlled, randomized trial with three months of follow up and intention to treat analysis

Study question: Does oral nimodipine (60mg every 4 hours) decrease the incidence of cerebral ischemic and infarction anew after aSAH

Site of study: Four regional neurosurgical units in the United Kingdom

Study population**:** June 1985 – September 1987, 554 patients recruited out of 1115 with confirmed subarachnoid hemorrhage confirmed by LP or CTH, or both.

Inclusion criteria: Patients admitted to hospital within 96 hours after onset of symptoms and signs of aSAH

Exclusion criteria: Admission to neurosurgical units more than 96 hours after aSAH, pregnancy, major renal, hepatic, or pulmonary disease; pre-existing cardiac decompensation (within six months), recent MI, < 18 years old, and SAH that produced coma in the week preceding most recent aSAH

Intervention: Treatment with either oral Placebo (n=276) or oral Nimodipine (n=278, 60mg every 4 hours) starting 96 hours after ictus and continued for a total of 21 days.

Primary outcome: Incidence of cerebral infarction and ischemic neurological deficits and outcome three months after entry

Clinical Monitoring:

1. Severity of aSAH graded by World Federation of Neurological Societies aSAH grading (Grade I – V, with V being equal to GCS of 3-7)
2. CTH performed within 24 hours after admission to trial and repeated as needed
3. Hemodynamics and neurological exam were aggressively monitored while hospitalized
4. Minimum criteria to define deterioration was either development of focal neurological signs or decline by one point on GCS for > 6hrs.

5. All episodes of deterioration and all patients whose outcome at 3 months was not good were assessed regularly by a blinded review committee comprising of representatives from each center. Cause of deterioration was aggressively worked up and classified as rebleed, cerebral ischemia or infarction, or other.
6. Outcomes was assessed at least three months after entry to trial according to five-point GCS scale (see above) by a physician not involved in patient's early aSAH care.
7. Patients who were dead or disabled at three months were assessed as to whether the cause was from the initial bleed, cerebral ischemia or infarction, rebleeding, or other

Results: Baseline characteristic data showed that Nimodipine-treated patients had a higher prevalence of hypertension, neck stiffness and non-reacting pupils; placebo-treated patients more often had a history of cardiovascular disease and tobacco use. Overall, nimodipine reduced the number of primary outcome events (number of cerebral infarcts) by 34% ($p = 0.003$). Nimodipine also reduced the number of secondary outcome events, namely the incidence of poor outcome (dead, vegetative state, and severely disabled) by 40% ($p < 0.001$). The principal reason for this improvement in overall outcome was attributable to a reduced incidence of delayed cerebral ischemia (other causes of death/disability were similar among the 2 treatment groups). A total of 103 patients died within 90 days of starting treatment, 43 in nimodipine group and 60 in placebo group. Nimodipine did not affect the incidence of rebleeding however there were not many rebleeds in this study to begin with. Finally, 27 patients had documented severe adverse reactions (17 for nimodipine, 10 for placebo). The highest number of events were for cardiovascular and hepatobiliary effects in both arms.

Conclusion: Overall, this study showed that oral nimodipine, at a dose of 60 mg every 4 hours, is well tolerated, reduces the likelihood of cerebral infarction, and improves outcomes after aSAH; this appears to hold true for all clinical grades of aSAH. Ultimately, this landmark study equipped neurointensivists with a neuroprotective agent to help prevent delayed cerebral ischemia after aSAH, and consequently improve long term outcomes. Further research regarding adequate dosing of nimodipine (IV or PO) or timing of medication is underway. The mechanism of action of this drug is unclear but the brain uses calcium for many processes specifically in controlling cerebrovascular smooth muscle. Regardless, in patients suffering from aSAH, early securement of an aneurysm and prophylactic administration of oral nimodipine are now considered standard of care in their acute management.

Summary created by Amit Mehta, MD