



# Alfred ICU Journal Club Review of “Pickard et al, 1989: British aneurysm nimodipine trial”

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## THE QUESTION

Does oral nimodipine reduce the incidence of cerebral infarction and poor outcomes (death and severe disability) after subarachnoid haemorrhage (SAH)?

## STUDY DESIGN

### TYPE OF STUDY

Randomised double blind placebo controlled trial involving 4 neurosurgical centres in the UK

### POPULATION

n = 554 from population of 1,115 patients admitted with SAH, confirmed by lumbar puncture (LP) or CT head or both

### Inclusion criteria

Patients admitted to a neurosurgical centre within 96 hours of onset of signs/symptoms

Diagnosis of SAH confirmed by LP/CT or both

### Exclusion criteria

Pregnancy

Major renal/hepatic/cardiac disease

Myocardial infarction in preceding 6 months

Age < 18 years

SAH producing coma in week preceding most recent SAH

original author and source are credited.



Patient or relative unwilling to consent

## INTERVENTIONS/ COMPARISONS

Nimodipine 60mg q4h orally, or via nasogastric tube, versus placebo

Treatment was started within 96 hours of onset of symptoms and continued for 21 days

## OUTCOMES

### Primary outcome

Incidence of cerebral infarction as determined by a drop in GCS of > 1 point or new focal neurological deficit lasting more than 6 hours

Absolute risk reduction of 11% in incidence of cerebral infarction in the treatment group compared with the control group (22% versus 33%,  $p=0.003$ ; relative risk reduction of 34%). This persisted after adjusting for potential imbalance of independent poor prognostic factors between groups.

This corresponds to a number needed to treat (NNT) = 9; i.e. if 9 patients are treated with oral nimodipine within 96h of subarachnoid haemorrhage, one patient will be prevented from developing cerebral infarction.

### Secondary outcomes

Outcome at 3 months was defined as poor outcome (Death, Persistent Vegetative State, Severe Disability) or good outcome (Good recovery or moderate disability)

Absolute risk reduction of 13% in incidence of poor outcome in the treatment group compared with the control group (20 vs 33%,  $p< 0.001$ ; relative risk reduction of 40%). This persisted after adjusting for potential imbalance of independent poor prognostic factors between groups

No significant difference in mortality between the two groups

No difference in the incidence of vasospasm between the two groups

Nimodipine was well tolerated

## COMMENTARY AND CRITICISMS

### *Strengths*

1. Good randomisation with blinding maintained throughout
2. Follow-up was complete
3. Sample size was sufficient
4. There was imbalance between groups in prevalence of known poor prognostic factors but this was adjusted for in their analysis
5. Minimal but justifiable exclusion criteria
6. The cut off of 96 hours was appropriate given prophylactic nature of nimodipine effect and high incidence of cerebral ischaemia on Day 5-15
7. The study utilised ischaemia rather than vasospasm as the outcome measure, which is appropriate given that most vasospasm is asymptomatic and difficult to detect, and nimodipine may have beneficial effects other than vasodilation

### *Criticisms*

1. Lack of documentation of how other parameters that may affect incidence of delayed cerebral ischaemia (DCI) were managed (e.g. blood pressure and fluid management)
2. There was a single patient who was excluded after randomisation and not included in the statistical analysis..... Strictly speaking, this patient should have been included on an intention-to-treat basis
3. There was a higher incidence of DCI in placebo group than predicted, which was not addressed in the discussion section of the article
4. Optimal duration of therapy was not clearly determined as 130 patients stopped treatment early
5. There are concerns over the applicability of this study to our patients today, who receive modern therapies:

Surgical intervention was performed significantly later in this study than it is today and induction of hypertension to treat DCI pre-operatively is inappropriate with an unsecured aneurysm

Interventional radiology is now much more widely available and no interventional radiology was used to treat DCI during this study. However, as this was a study of prevention of DCI rather than treatment, the result of the primary remains relevant

### **FINAL WORDS**

Prophylactic nimodipine via the enteral route is well tolerated and reduces delayed cerebral ischaemia post SAH and improves 3 month outcomes.

The mechanism of this beneficial effect is unclear, particularly as nimodipine was not associated with a decrease in vasospasm, as is the optimal duration of therapy.