Placebo-Controlled Trial of Nimodipine in the Treatment of Acute Ischemic Cerebral Infarction

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Nimodipine is a 1,4-dihydropyridine derivative that shows a preferential cerebrovascular activity in experimental animals. Clinical data suggest that nimodipine has a beneficial effect on the neurologic outcome of patients suffering an acute ischemic stroke. Our double-blind placebo-controlled multicenter trial was designed to assess the effects of oral nimodipine on the mortality rate and neurologic outcome of patients with an acute ischemic stroke. One hundred sixty-four patients were randomly allocated to receive either nimodipine tablets (30 mg q.i.d.) or identical placebo tablets for 28 days. Treatment was always started ≤48 hours after the acute event. The Mathew Scale, slightly modified by Gelmers et al, was used for neurologic assessment. Mortality rate and neurologic outcome after 28 days were used as evaluation criteria. We considered 123 patients to be valid for the analysis of efficacy. Mortality rates did not differ significantly between groups. Neurologic outcome after 28 days of therapy did not differ between groups. However, when only those patients most likely to benefit from any intervention (Mathew Scale sum score of ≤65 at baseline) were analyzed separately in post hoc–defined subgroups, the nimodipine-treated subgroup showed a significantly better neurologic outcome. This result suggests that some patients with acute ischemic stroke will benefit from treatment with nimodipine tablets. (*Stroke* 1990;21:1023–1028)

Although it is one of the leading causes of death and disability in the Western world, the treatment of cerebral ischemic infarction remains controversial. This controversy is mainly due to the fact that most therapeutic measures used in many centers, even those therapies used on a routine basis, have not been fully evaluated in adequate controlled clinical trials.[1]

Although the sequence of events that take place in cerebral ischemia is not completely understood, some key factors involve the release of neurotransmitters resulting from depolarization and the presynaptic influx of Ca^{2+}.[2] This allows speculation that pharmacologic intervention aimed at reducing the presynaptic and postsynaptic influx of Ca^{2+} could be beneficial in patients with acute cerebral ischemia.

Nimodipine is a calcium antagonist derived from the 1,4-dihydropyridine ring with a preferential cerebrovascular action.[3] Experimental studies have shown that the administration of nimodipine after complete cerebral ischemia improves neurologic outcome in dogs[4] and primates.[5] Studies of cerebral blood flow in patients with vasospasm after subarachnoid hemorrhage and patients with ischemic cerebral infarction suggest that nimodipine increases hemispheric blood flow in a dose-dependent manner without resulting in a steal phenomenon.[6] The results of an open study[7] and the results of a placebo-controlled trial reported up to now[8] show that treatment with nimodipine starting early after the onset of cerebral ischemic infarction favorably alters the neurologic and possibly the functional[8] outcome of such patients.

The aim of our study was to assess the influence of nimodipine on two predefined end points: the 28-day mortality rate and the neurologic outcome after 28 days of in-hospital treatment.

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Subjects and Methods

Four departments of neurology in Spain were responsible for recruiting, treating, and evaluating patients admitted for acute ischemic stroke between August 1984 and June 1987. The study protocol was approved by the clinical trial committees of the centers and by the Regulatory Board for Drugs and Health Care Products of the Spanish Ministry of Health before the start of the trial.

Patients >44 years old with acute ischemic stroke in the internal carotid artery territory, as diagnosed by clinical examination, were qualified for entry into the trial if they were seen ≤48 hours after stroke onset. The clinical diagnosis always had to be confirmed by an early computed tomogram performed during the first 3 days after qualifying.

Patients with acute myocardial infarction, renal failure, liver failure, severe systemic infections, poorly controlled diabetes mellitus, systolic arterial blood pressure of <100 mm Hg, or terminal malignancy were excluded from the study. Patients whose neurologic deficit recovered completely within 24 hours (transient ischemic attack), those with stroke-in-evolution, and those in coma were considered ineligible for the study. All patients with brain lesions other than infarction (such as subarachnoid hemorrhage and intracerebral hemorrhage) or special causes for the stroke (such as complicated migraine) were also excluded. Informed consent was obtained in every case from the patient or a responsible relative.

Patients entered into the study were randomly allocated to receive either oral nimodipine, one 30-mg tablet every 6 hours, or an identical placebo tablet. Treatment was started in all cases ≤48 hours after the onset of clinical manifestations of acute ischemic stroke and continued during 28 days in the hospital. The study protocol allowed the administration of prophylactic heparin (5,000 IU b.i.d.) and agents considered to be medically indicated in cerebral edema as well as cardiovascular drugs other than calcium antagonists and antibiotic or anxiolytic medications when needed.

The Mathew Scale,[9] as slightly modified by Gelmers et al,[8] was used as the main criterion for assessing the neurologic outcome of the patients. Neurologic deficit was rated at entry into the study (baseline) and after 1, 3, 5, 7, 14, 21, and 28 days of treatment. A Mathew Scale sum score of ≤65 indicates moderate-to-very severe deficit.

For the analysis of homogeneity of the groups we used Student's *t* test for age, the Mann-Whitney test for baseline Mathew Scale scores, and the χ^2 test for sex differences. Mortality was compared using survival tables.

When comparing changes in neurologic deficit, it is important to take into account that the Mathew Scale is an ordinal one with upper and lower limits. The greatest possible increase in the Mathew Scale score depends on the baseline score; therefore, a relative change in the neurologic deficit is defined as $x=(y_t-y_0)\div(100-y_0)\times 100\%$ for improvements (i.e., $y_t \geq y_0$) and $x=(y_t-y_0)\div y_0 \times 100\%$ for deteriorations (i.e., $y_t<y_0$), where y_0=Mathew Scale sum score at baseline and y_t=Mathew Scale sum score after 28 days. Modification of the denominator for improvements and deteriorations is necessary to get the same range of possible changes between 100% and −100% independent of the individual's baseline score. A similar method was used for each item of the Mathew Scale. For those patients with only a baseline score (i.e., patient withdrew from the study), the numerator was calculated as 0 because no other information on the clinical course of the patient was available. Relative reduction of neurologic deficit was analyzed using a nonparametric two-sample test (Breslow statistic).

Table 1. Stroke Patients Excluded From Efficacy Analysis by Treatment Group

Reason for exclusion	Treatment group	
	Nimodipine	Placebo
Treatment initiated too late	5	4
Wrong diagnosis and concomitant disease not allowed	7	5
Brain computed tomogram not available	2	3
Coma	3	1
Insufficient duration of treatment and/or lost to follow-up	6	5

Results

We entered 164 patients, of whom 81 (43 men and 38 women) received nimodipine; the remaining 83 patients (43 men and 40 women) received placebo. The groups were well matched for age, height, and weight distributions. The average age was 71.9 (range, 45–92) years in the nimodipine group and 72.3 (range, 50–92) years in the placebo group.

Of the 164 patients entered into the study, 41 were excluded blindly from the efficacy analysis by the Review Committee (Table 1); the other 123 (58 receiving nimodipine and 65 receiving placebo) were considered valid for the efficacy analysis (Table 2).

No significant differences were observed between groups for severity of the initial neurologic deficit according to the Mathew Scale sum scores at baseline (Table 3). Mortality rate after 28 days was 10.3% (six of 58) in the nimodipine group and 15.4% (10 of 65) in the placebo group. No sex-specific differences in mortality rates were detected. The causes of death by clinical findings in both groups are shown in Table 4. Including all 164 patients randomized (intention-to-treat analysis), mortality was 14.8% (12 of 81) in the nimodipine group and 16.9% (14 of 83) in the placebo group.

In an exploratory analysis, patients with moderate-to-very-severe neurologic deficit at baseline were looked at separately (Table 5). Among these patients, mortality rate was 12.5% (six of 48) in the nimodipine subgroup and 20.8% (10 of 48) in the placebo sub-

TABLE 2. Characteristics of 123 Stroke Patients Considered Valid for Efficacy Analysis by Treatment Group

	Treatment group	
Characteristic	Nimodipine (*n*=58)	Placebo (*n*=65)
Age (mean±SD yr)	71.8±10.0	71.9±10.1
Sex		
Female	25	28
Male	33	37
Location of lesion		
Left hemisphere	38	38
Right hemisphere	20	27
Risk factors		
Hypertension	16	14
Diabetes mellitus	8	13
Cardiac disorders	40	35

Data are number of patients unless noted.

group (difference not significant); all patients who died during the treatment period had a Mathew Scale sum score of ≤65 at baseline.

There was no significant difference between groups in relative change in neurologic deficit for all 164 randomized patients (intention-to-treat analysis, p=0.31) or for the 123 patients valid for efficacy analysis (p=0.15, Figure 1). In the exploratory analysis, however, there was a significant difference (calculated by the Breslow statistic) in favor of nimodipine (p<0.025, Figure 2). Approximately 40% of the nimodipine-treated patients had a reduction of neurologic deficit of at least 50%, whereas <10% of the placebo-treated patients showed such a reduction.

A descriptive analysis of the relative change for each item of the Mathew Scale was also performed for the 123 patients valid for efficacy analysis. Those items

TABLE 3. Severity of Initial Neurologic Deficit in 123 Stroke Patients Considered Valid for Efficacy Analysis as Baseline Mathew Scale Sum Score

		Treatment group	
Severity	Score	Nimodipine (*n*=58)	Placebo (*n*=65)
Mild	>65	10	17
Moderate to very severe	≤65	48	48

Data are number of patients.

TABLE 4. Causes of Death Among 164 Stroke Patients Randomized by Treatment Group

	Treatment group	
Cause of death	Nimodipine (*n*=81)	Placebo (*n*=83)
Bronchopneumonia, pulmonary embolism	4	4
Heart failure, myocardial infarction	2	2
Brain edema	5	8
Septicemic shock	1	0

Data are number of patients.

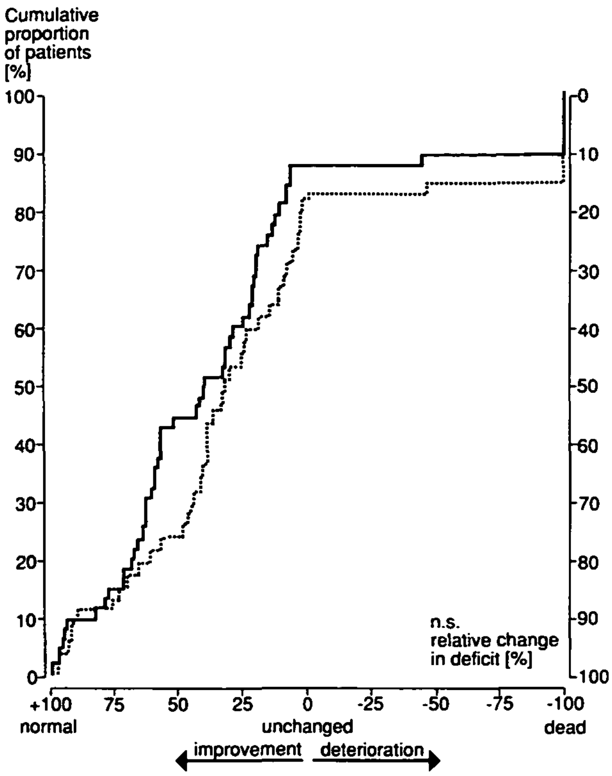

FIGURE 1. *Cumulative frequency diagram of relative change in neurologic deficit for 123 stroke patients valid for efficacy analysis. —, Nimodipine group* (n=58)*; - - -, placebo group* (n=65)*.*

showing the greatest differences between groups are outlined below.

Thirty-nine patients in the nimodipine group and 43 in the placebo group had a disability score of 7 (severe impairment) at baseline. Of these patients, 13 (33%) in the nimodipine group recovered completely (disability score of 28) or had only a slight impairment (disability score of 21) after 28 days compared with only six patients (14%) in the placebo group. By contrast, in the nimodipine group only 10 patients had a severe impairment after 28 days of treatment and only four patients died (36%) compared with 18 and 10 patients, respectively (65%), in the placebo group.

With regard to aphasia, 33 patients in each group had a score of 0–10 at baseline. Twenty-one patients (64%) in the nimodipine group and eight (24%) in the placebo group reached a score of 15–23 after 28 days of treatment.

When motor power of the affected side was evaluated, 14 of 40 patients (35%) in the nimodipine group with an unfavorable score (0–4 points: sum of upper and lower limb) at baseline reached a final score of 8–10 points, while only eight of 48 patients (17%) in the placebo group in the same condition at baseline improved.

No differences in mean systolic or diastolic blood pressure or heart rate were observed between groups (Figures 3–5).

TABLE 5. **Relative Change in Neurologic Deficit After 28 Days for 123 Stroke Patients Valid for Efficacy Analysis by Mathew Scale Sum Score at Baseline**

	Score				
	≤65		>65		
Relative change	Nimodipine (n=48)	Placebo (n=48)	Nimodipine (n=10)	Placebo (n=17)	Total
Death	6	10	0	0	16
Deterioration	1	1	0	1	3
Improvement					
0–25%	14	14	2	2	32
25–50%	8	19	1	2	30
>50%	19	4	7	12	42

Data are number of patients.

Adverse reactions in the 164 patients initially entered into the study were also recorded. Gastrointestinal bleeding occurred in two patients in each group. Four nimodipine-treated patients suffered adverse effects considered to be probably or possibly related to therapy. These cases included one patient with gastrointestinal bleeding who had received dexamethasone concomitantly, one patient with a vagal reaction, one patient with a maculopapulous skin reaction, and another patient with abdominal distension.

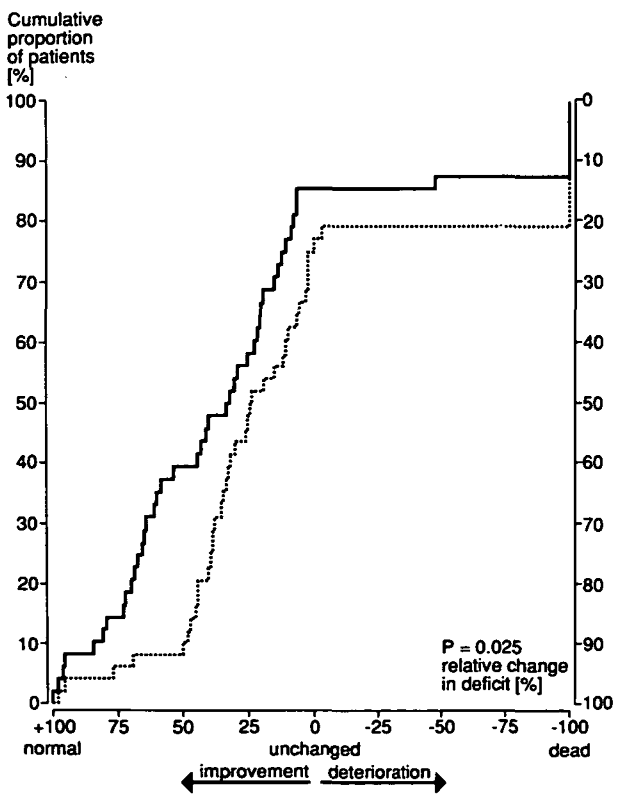

FIGURE 2. *Cumulative frequency diagram of relative change in neurologic deficit for 96 stroke patients valid for efficacy analysis with Mathew Scale sum score at baseline of <65. —, Nimodipine group* (n=48); *- - -, placebo group* (n=48).

Discussion

Some aspects of the design of a clinical trial of acute ischemic cerebral infarction must be taken into account before undertaking the clinical study. The inclusion criteria must be sufficiently permissive to allow a reasonable rate of patient recruitment while being sufficiently restrictive to ensure homogeneity of the sample. Another difficulty to bear in mind is the selection and definition of the evaluation criteria. Although much has been discussed and many scales have been proposed, studies designed to validate the evaluation system have only recently been carried out.[10] We used the Mathew Scale because it is a relatively quick and simple method of assessing neurologic status and, particularly, because it was used in the first double-blind, placebo-controlled trial of nimodipine reported in the literature.[8]

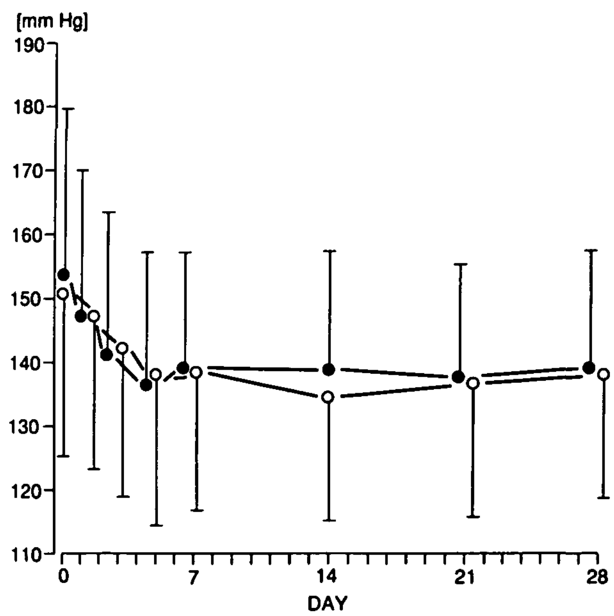

FIGURE 3. *Graph of mean±SD systolic blood pressure during treatment period for 123 stroke patients valid for efficacy analysis.* ●, *Nimodipine group* (n=58); ○, *placebo group* (n=65).

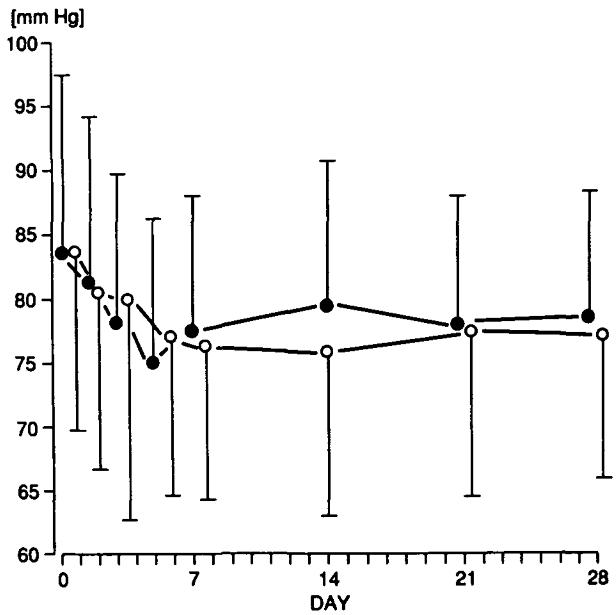

FIGURE 4. *Graph of mean±SD diastolic blood pressure during treatment period for 123 stroke patients valid for efficacy analysis.* ●, *Nimodipine group* (n=58); ○, *placebo group* (n=65).

A relevant problem arises when describing the outcome of a study using statistical methods based on mean values. The mean disability of survivors improves, whereas more severely ill patients die and do not contribute to the final mean. This indicates that a single study is not necessarily adequate to show primary effects in both mortality and neurologic outcome at the same time; if spontaneous mortality is high and if active treatment reduces it significantly, the treated group is then soon at a disadvantage[11] from the standpoint of neurologic or functional recovery. This was taken into account by our transformation of the Mathew Scale scores.

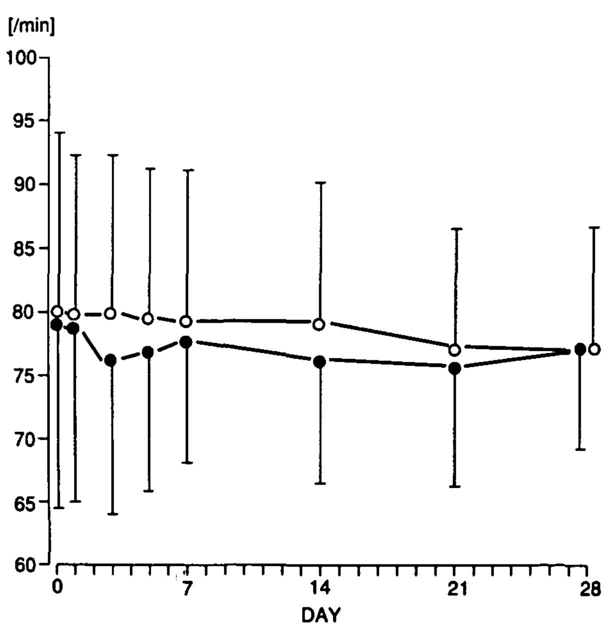

FIGURE 5. *Graph of mean±SD heart rate during treatment period for 123 stroke patients valid for efficacy analysis.* ●, *Nimodipine group* (n=58); ○, *placebo group* (n=65).

Concomitant medication must also be considered. Because no participating center used a standard therapy for treating acute cerebral infarction, the protocol allowed the concomitant administration of any drug judged indicated for the complications frequently seen in these patients. Concomitant therapies were similarly distributed in both groups; it is very unlikely that concomitant therapies contributed to the differences in favor of nimodipine.

A priori prognostic stratification of patients in clinical trials of cerebral infarction is often recommended. We used no randomization stratification according to severity, but the baseline neurologic impairment was similar in both groups (as shown in Table 3). At the time of analysis of neurologic outcome, two categories of patients were considered (those with a Mathew Scale sum score of ≤65 and >65 at baseline). This categorization was chosen because previous observations[7,8] have shown that nimodipine is better than placebo only in patients with an at least moderate-to-severe baseline neurologic deficit; we confirmed this restriction. The restriction of nimodipine's efficacy could be explained by the fact that patients with a relatively normal baseline neurologic status (Mathew Scale sum score of >65) have a spontaneous rate of recovery so high that no additional effect due to nimodipine therapy can be measured. In patients with a baseline Mathew Scale sum score of ≤65, the administration of nimodipine had a significant effect on neurologic outcome. This beneficial effect was clinically measurable and is similar to that reported by Gelmers et al[8] in the first double-blind placebo-controlled trial of oral nimodipine in patients with acute cerebral infarction.

Nimodipine-treated patients showed a trend toward a lower 28-day mortality rate, particularly in the subgroup with moderate-to-very severe neurologic deficit at baseline. However, and in contrast to the findings of Gelmers et al,[8] this difference in mortality rate was not significant.

It is worth noting that nimodipine had no significant effect on systemic hemodynamics, which is in agreement with the findings of other clinical trials.[12,13]

The mechanism responsible for the beneficial effect of nimodipine in patients with acute ischemic cerebral infarction is not completely understood and may be multiple. On one hand, nimodipine prevents the postischemic reduction of cerebral blood flow after transient interruption of cerebral perfusion seen in animals.[14,15] Some experimental evidence shows that the immediate failure of basic neuronal functions depends heavily on residual blood flow. Total failure of these functions occurs below a critical blood flow threshold,[16] while at higher blood flows cerebral infarction occurs after a certain time.[17]

The ischemic cerebral territory that shows a borderline blood flow was named the ischemic penumbra.[18]

Complicated phenomena that tend to reinforce the effects of the initial ischemic insult and biochemical reactions that eventually lead to neuronal death occur in this area.[19] A recently reported dysregulation of calcium homeostasis in ischemic cells appears to be the final pathway responsible for cell death.[20] Apart from its vascular effects, the demonstration of specific binding sites for [^{3}H]nimodipine in human cerebral tissue[21] and the behavioral changes observed in animals treated with nimodipine[22] suggest that this agent acts directly on the cerebral tissue. In our trial, differences in the causes of death between groups may be relevant, with more deaths due to central nervous system complications, particularly cerebral edema, in the placebo group. Whether this finding is related to the mechanism of action of nimodipine or to any other possible explanation remains at present merely speculative.

Although there is evidence that cerebral ischemia and especially the ischemic penumbra are susceptible to therapeutic intervention,[2] the time interval after the acute ischemic event during which such intervention is useful in humans is not clear. However, an intuitive and reasonable inference is that sooner is probably better. The maximum interval of 48 hours that we used was chosen because it was clinically feasible and similar to that used in other studies.[7,8] Whether our results obtained with nimodipine can be extrapolated to other calcium antagonists remains to be elucidated since, as far as we know, no controlled clinical trials with other agents of this group have yet been reported.

Neurologic outcome after 28 days of therapy did not differ between groups. However, when only those patients most likely to benefit from any intervention (those with a Mathew Scale sum score of ≤65 at baseline) were analyzed separately post hoc, the nimodipine group had a significantly better neurologic outcome. This result suggests that some patients with acute ischemic stroke would benefit from treatment with nimodipine tablets.

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KEY WORDS • cerebral ischemia • mortality • nimodipine