

## A RANDOMIZED DOUBLE-BLIND CONTROLLED STUDY OF NIMODIPINE IN ACUTE CEREBRAL ISCHEMIC STROKE

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**Abstract :** A randomized placebo controlled double-blind clinical trial of nimodipine was conducted in 31 patients of acute cerebral infarction. Nimodipine was administered in dosage of 120 mg/day for 28 days. Treatment was begun within 48 hours of ischemic stroke. Diagnosis was confirmed by computed tomographic (CT) scan. Similar number of patients (control) received placebo. Neurological assessment was done at the time of entry into the trial, and after 4 weeks, by using Mathew's scale. After four weeks of treatment with nimodipine or placebo, Mathew's scale score improved significantly ( $<0.001$ ) in both groups, but difference in mean score between two groups was insignificant ( $>0.05$ ). However, significant difference ( $<0.05$ ) was noted in relative change in neurological deficit (mean X-value) of two groups. The nimodipine group had higher value in scores on Mathew's scale. No adverse reaction, was observed in either group. The study suggests a beneficial effect of nimodipine in acute cerebral ischaemia.

**Key words :** cerebral infarction      stroke      nimodipine  
calcium channel blockers      calcium antagonists

### INTRODUCTION

Of the various medical therapies that have been evaluated for the management of acute ischemic stroke, calcium antagonists appear to be the most promising. It has been observed that increase in internal calcium concentrations stimulates a number of calcium-dependent molecular processes leading to the formation of several mediators of neurotoxicity such as highly toxic oxygen free radicals, which damage the neuronal membrane and cause its disintegration. Therefore, blockade of the calcium overload

may limit secondary damage in the penumbral zone of ischemia (1). The major experience to date has been with nimodipine which has less systemic effects than the other calcium channel blockers, and penetrates the blood brain barrier well (2, 3). In a large multicentric trial of nimodipine in subarachnoid haemorrhage, infarction was reduced by 34% and poor outcome by 40% (9). Early trials for ischemic stroke using nimodipine showed decreased mortality when treatment was begun within 24 hours of stroke onset, but issue of functional recovery remained inconclusive

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(5). The present study was designed to determine the safety and efficacy of nimodipine in hospital based Indian patients of acute cerebral ischemia.

## METHODS

Patients with acute ischemic stroke within preceding 48 hours were included in the trial. They presented with acute onset of hemiplegia of either side with or without aphasia. The clinical diagnosis was confirmed by an early computed tomographic (CT) scan which showed hypodense lesion in the territory of either middle cerebral artery. The patients were excluded if they had only transient neurological deficiency (persisting < 24 hours), coma (Glasgow coma scale score < 10), intracranial haemorrhage, tumor, infection, trauma, need for assisted ventilation, pregnancy, severe hypertension (diastolic blood pressure > 120 mm Hg),

hepatic or renal dysfunction. Informed consent was taken from each case. Protocol was cleared by institutional Ethics Committee.

Eighty patients out of 138 patients of stroke admitted in Neurology/Medical Ward KG's Medical College, Lucknow (between May 1991 to June 1992) were selected. Patients were randomly allocated to receive either code - A drug (nimodipine 30 mg), or code - B drug (placebo). In nimodipine group there were 39 patients, and 41 patients were in placebo group. The tablets in both the groups were administered at 6 hourly interval. The treatment was started in all cases within 48 hour after the acute event, and was continued for 28 days, while patients remained hospitalized. other routine management (antihypertensive, hypolipaedimics, platelet antiaggregants, haemorrhological drug, oedema reducing measures etc.) were given in both the groups

TABLE I : Demographic characteristics of patients of both the groups.

Characteristic	Group (A) n = 31	Group (B) n = 31
Age years (mean±SD)	53.52±12.19*	51.±10.47
Sex		
Male	23	24
Female	8	7
Risk Factors		
Hypertension (diastolic BP > 90 mm Hg)	7	9
Mean diastolic BP of whole group (mean ± SD mm Hg)	100.67±13.92*	98.30±20.32
Diabetes mellitus	6	3
Cardiac disorders @	3	3
Transient ischaemic attacks @@	6	6
Smoking (cigarette and / or biri)		
Current Smoker	12	13
Ex-Smoker	16	13
Non-smoker	3	5

\*Different (group A Vs group B) were insignificant (P > 0.05).

@Patients had present and / or past evidence of coronary artery disease.

@@One or more episode of focal ischemic cerebrovascular event in past, lasting > 24 hours.

as per clinical decision. In addition to CT scan, complete haemogram, urinalysis, serum biochemical parameters, X-ray chest and electrocardiogram were obtained in each case of both the groups (Table I). Eight patients in nimodipine group and 10 patients in placebo group dropped out.

The Mathew's scale (6) as modified by Gelmers et al, (5) was used for assessing the neurological outcome of the patient. Patients were seen daily for a formal but brief neurological examination during the in-hospital phase. Detailed examination was performed at the time of inclusion and at 4 weeks.

When comparing changes in neurological defects, it was important to take into account that the Mathew's scale was an

## RESULTS

No significant difference ( $P > 0.05$ ) was observed for initial neurological deficit between nimodipine group and placebo group. None of the patient showed a decrease in the Mathew's scale score. No mortality was observed in either of the group over 4 weeks of follow-up. Group analysis revealed significant improvement ( $P < 0.001$ ) in Mathew's scale score for both groups after 4 weeks. The difference in mean score at this stage was insignificant ( $P < 0.05$ ) between groups. However, significant difference ( $P < 0.05$ ) was noted in relative change in neurological deficit (X-value). Nimodipine group had higher mean value (Table II). No noticeable difference in blood pressure or heart rate were observed. No adverse reaction which could be

TABLE II : Change in Mathew's scale score of both the group at 4 weeks.  
(Mean  $\pm$  SEM)

Group	n	Baseline score	At 4 weeks	Relative change in neurological deficit 'X'
Group A (nimodipine)	31	41.87 $\pm$ 2.02	63.82 $\pm$ 2.19**	48.54 $\pm$ 2.56*
Group B (placebo)	31	45.87 $\pm$ 1.73	60.78 $\pm$ 2.39**	36.95 $\pm$ 2.53

\* Difference significant ( $<0.05$ ) group A Vs group B.

\*\*Difference was significant in comparison to baseline value ( $P < 0.001$ ).

ordinal one with upper and lower limits. The greatest possible increase in this score would be dependent upon the baseline score. Therefore, a relative change in the neurological defects is defined as  $X = 100(Y_4 - Y_0) / (100 - Y_0)$  for improvement (i.e.  $Y_4 > Y_0$ ), and  $X = 100(Y_4 - Y_0) / Y_0$  for deteriorations (i.e.  $Y_4 < Y_0$ ), where  $Y_0$  and  $Y_4$  are baseline score and score at 4 weeks respectively. Statistical analysis was done using paired and unpaired students 't' tests.

attributed to the trial drug was observed in either group.

## DISCUSSION

Although the time interval after acute ischaemic event during which the ischaemic penumbra responds to therapeutic, intervention in human is not yet clear, however, the sooner it is begun the better. The maximum interval of 48 hours was chosen for our study because it was

clinically feasible, and was similar to that used in other studies.

Analysis of the change in the neurological status revealed that at 4 weeks the patients of both the groups improved significantly. However, the relative change in neurological deficit was significantly higher for nimodipine group. Similar trial conducted by "Nimodipine study group" (7) could not observe significant difference in mortality or neurological function, but, subgroup analysis of those patients treated with 120 mg/day within 18 hours of stroke onset showed better outcome and 30% reduction in frequency of deterioration. The observation of our study are also in confirmity of this series. A Dutch trial (5) of oral nimodipine found that the drug reduced mortality in men and had a beneficial effect in reducing the clincial deficits in patients with moderate to severe neurological abnormalities. Another trial observed disappointing results, subgroup analysis showed some benefit if given early (8).

During ischaemia, excitatory neurotransmitters are released that allow calcium entry into neurons, activating a number of proteolytic enzymes. The result may be the production of free radicals which can cause neuronal toxicity. Calcium channel blockers reduce or prevent calcium entry into neurons during ischaemia and, thus avoid the toxic effect of intracellular calcium (9, 10). The results of this study indicate that nimodipine therapy does have the potential to improve the outcome in acute ischaemic stroke.

Through beneficial role of nimodipine in the management of acute cerebral ischaemia is suggested, yet due to previous conflicting reports, further confirmation in larger number of patients is required.

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