Role of Oral Nimodipine in the Management of Acute Cerebral Ischemic Stroke

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Abstract

In order to study the beneficial effect of oral nimodipine, fifty CT confirmed, mild to moderately severe ischemic stroke patients were divided into two groups of 25 each, with the study group receiving nimodipine in the doses of 120 mg per day. The control group of 25 patients did not receive nimodipine. The treatment was continued for 21 days. The initial and final neurological assessment was made according to modified National Institute of Health Stroke Scale (MNIHSS) and percentage change in score at day 21 (PRC21) was calculated. The baseline parameters and neurological score in both the groups were identical. Absolute Score (9.56 ± 6.55 vs 13.6 ± 8.14, p < 0.05) and percentage change in score at day 21 (36.23 ± 29.04 vs 23.44 ± 23.74, p < 0.05) was better in nimodipine group as compared to the control group. On subset analysis it was also discovered that the patients who received nimodipine within 24 hours of onset of stroke fared better. Hence it is concluded that oral nimodipine in the divided doses of 120 mg per day is definitely useful in improving the neurological recovery of mild to moderately severe cases of ischemic stroke, provided they receive the drug within 24 hours of the onset of stroke.

Keywords: Cerebrovascular disorders, Ischemic cerebral stroke, Nimodipine, National Institute of Health Stroke Scale (NIHSS)

INTRODUCTION

Stroke constitutes nearly 1% to 2% of all hospital cases, 1% to 4.5% of all cases admitted to medicine wards and 15 to 20% of all neurological admissions in India. It is also a major cause for morbidity and mortality, both in the developed and developing countries. The objectives of medical treatment in its management are to restore perfusion of blood to compromised areas of the brain and to prevent secondary ischemic events. When cerebral perfusion rate decreases below a threshold of about 20 ml/mnt/100 g, cerebral function is impaired reversibly, but further fall to less than 10 ml/mnt/100 g leads to irreversible functional impairment. In the peri-infarction zone, the perfusion rate is between these two levels and this area can be salvaged by timely medical treatment.

Cerebral ischemia leads to a massive shift of calcium from the extracellular to the intracellular space, along with decrease in adenosine triphosphate (ATP) levels. This results in calcium overload that has detrimental effect on cell metabolism and it also causes increased vascular resistance. Nimodipine is a cerebro-selective, voltage dependent slow calcium channel blocker drug belonging to the dihydropyridine group. It has been shown to prevent spasm of the cerebral arteries as well as prevent post-ischemic impairment of regional cerebral blood flow. Its use has been found to sig-
nificantly improve the prognosis in patients of stroke by many workers,5-8 though others were not of the same view.9,10

As the controversy on the role of nimodipine in ischemic stroke persists and only a few studies have utilized investigations like CT scan and neurological assessment scale to evaluate the role of nimodipine, it was decided to carry out a well-planned study, keeping in mind the above short-comings.

**MATERIALS AND METHODS**

This study consisted of 50 clinically diagnosed and CT proved cases of acute ischemic cerebral infarction, seen within 48 hours of onset. The study was approved by the ethical committee of the hospital and an informed consent was taken from the patient or a close relative for the purpose of investigations and treatment. Only mild to moderately severe cases of ischemic stroke who were not in coma were included in this study as the neurological scoring scale could not be applied in the unconscious patients.

**Study Protocol:** of the 50 patients selected for this study, 25 were alternately allocated to receive nimodipine (Group A) on a fixed oral dose of 30 mg every 6 hours i.e. 120 mg/day, along with necessary symptomatic treatment for 21 days. Other 25 patients formed the control group (Group B). The neurological assessment was rated according to the modified National Institute of Health Stroke Scale (MNIHSS) at the beginning and at the end of the study period.11

**Exclusion Criteria:** care was taken to exclude patients suffering from acute myocardial infarction, renal failure, liver failure, severe systemic infections, poorly controlled diabetes mellitus, systolic arterial blood pressure < 100 mmHg or terminal malignancy. Patients of transient ischemic attacks (TIA) were also excluded. Patients who presented in coma or subsequently lapsed into coma were also excluded because of inapplicability of the stroke scale. Patients presenting with stroke following subarachnoid or intracerebral hemorrhage, thromboembolism and stroke caused by infections, tumors, complicated migraine or partial epilepsy were also excluded.

**Methods:** all patients were subjected to a thorough clinical examination and routine investigations like Hb, TLC, DLC, ESR, urine analysis, blood urea, sugar, serum electrolytes, cholesterol, uric acid, X-ray chest and ECG. Echocardiography and CECT scan head and the neck were also carried out in all the subjects. The neurological status was assessed using the modified National Institute of Health Stroke Scale. The result of each part of the assessment was added to give the final score which could vary from 0 (no impairment) to 82 (maximum deficit). Patients were evaluated at day 1, 3, 5, 7, 14 and 21. The percentage change (PRC) in score at day 21 was calculated (e.g. percentage change in score at day 21 (PRC21) = the absolute value of (Day 21 score-Baseline score) : Baseline score x 100).11

The data so collected was analyzed using appropriate standard statistical methods (paired 't' test for comparison of change in neurological score in the same group and unpaired 't' test for comparison between the study and control groups).

**RESULTS**

The mean age of the fifty ischemic stroke patients was 51.81 years and the sex ratio was approximately 9:2. The nimodipine and the control group were comparable in their baseline characteristic and symptomatology at presentation. One or more risk factors were present in as many as 64% of patients in group A and 72% in group B. Smoking was the commonest risk factor (40%) followed by hypertension (20%). A recent ICMR study has found anemia to be a risk factor for stroke in Indian patients. In the present study, 58% of patients in group A and 60% in group B were found to have hemoglobin level less than 12 g%.

Majority of the patients in both the groups had lesions in the temporal or temporo-parietal region, with two patients showing ventricular effacement and midline shift on CT scan brain. One patient had bilateral occipital infarct.

The effect of nimodipine on systolic and diastolic blood pressure was negligible. No significant side effects of nimodipine were observed during therapy.

**Neurological Outcome:** assessment by modified National Institute of Health Stroke Scale at baseline i.e. Day 1 of study, revealed no statistically significant difference in the score in the two groups, but at day 21 i.e. after therapy, there was statistically significant difference in the absolute values of the neurological score (p < 0.05) (Figure 1), with patients in the nimodipine group showing better score (9.56 ± 6.55 vs 13.6 ± 8.14). On comparing with baseline values, significant improvement in the neurological score started
by day 3 and continued till day 21 in both the groups (p < 0.001) (Table 1). The change in the neurological score in the group receiving nimodipine was better than the control group, though it was not statistically significant (5.64 ± 4.51 vs 3.80 ± 3.64). The percentage change in score at day 21 (PRC21) was significantly more in the nimodipine group (36.23 ± 29.04 vs 23.44 ± 23.74, p < 0.05) (Figure 2).

Table 1. Neurological Score in Nimodipine and Control Groups.

<table>
<thead>
<tr>
<th>Day</th>
<th>Control Group</th>
<th>Nimodipine Group</th>
<th>'p' value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.40 ± 9.22</td>
<td>15.20 ± 8.32</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>17.12 ± 9.06*</td>
<td>14.52 ± 8.09**</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>16.60 ± 9.06**</td>
<td>13.60 ± 7.76**</td>
<td>NS</td>
</tr>
<tr>
<td>7</td>
<td>15.80 ± 9.13***</td>
<td>12.08 ± 6.81***</td>
<td>NS</td>
</tr>
<tr>
<td>14</td>
<td>13.96 ± 8.56***</td>
<td>10.64 ± 6.52***</td>
<td>NS</td>
</tr>
<tr>
<td>21</td>
<td>13.60 ± 8.14***</td>
<td>9.56 ± 6.55***</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

'p' value from the baseline in the same group - * <0.05, ** <0.01, *** <0.001

Figure 1. Neurological Score on Day 1 and Day 21 in the Nimodipine and Control groups.
Forty-eight percent (12/25) of patients in group A and 44% (11/25) of patients in group B entered the study within 24 hours of the acute event. It was found that on the whole, the patients in whom treatment was initiated early (within 24 hours), the percentage improvement in neurological score ($PRC_{21}$) was significantly more than those in whom treatment was initiated after 24 hrs ($48.91 \pm 27.29$ vs $20.48 \pm 22.89$, $p < 0.001$). Comparison within the same group revealed that percentage improvement in the neurological score ($PRC_{21}$) was significantly more in those who received nimodipine within 24 hours of stroke ($p < 0.001$).

**DISCUSSION**

Perhaps the most exciting advancement in the treatment of brain ischemia has been the introduction of drugs that block the entry of calcium into the cells. The beneficial effect of nimodipine on the outcome of acute ischemic stroke has been documented by some other studies. We used the modified National Institute of Health Stroke Scale to assess the neurological outcome in the present study.

The patients in this study, both rural and urban, presented on an average 27 hours after the onset of acute ischemic stroke. The group given nimodipine and the control group were comparable in baseline data, risk factors and neurological deficit. The age, sex and risk factor profiles of the patients, as well as the neurological deficit at the onset in this study were comparable with other studies.6,7,9,12

At baseline, there was no significant difference in the neurological scores in the two groups. On day 21, there was statistically significant improvement in both the groups, irrespective of whether given nimodipine or not. However, there was statistically significant difference in the percentage improvement on day 21 ($PRC_{21}$) in the neurological score between the patients given nimodipine and the control group ($p < 0.05$). On further analysis, it was found that if treatment with nimodipine was started within 24 hours of the acute event, there was significant improvement in neurological score than if treatment was started after 24 hours ($p < 0.001$). The drug was well tolerated in the dose of 120 mg/day without any side effects.

Our study is comparable to others in many but not in all aspects. The main difference between our trial design and others' was in the neurological score used, inclusion of CT proved cases only and the time of start of treatment. Most of our patients received treatment after 24 hours. The time-frame within which nimodipine should be given so as to have a beneficial effect varies widely in various studies. Gelmers ob-
served improvement with nimodipine when given within 24 hours\textsuperscript{12} and Paci et al\textsuperscript{8} observed improvement in patients given nimodipine within 12 hours of onset. Martinez-Vila et al observed benefit in the patients who has moderate to severe deficit and presented within 48 hours of stroke.\textsuperscript{7} On the other hand, Trust and American study groups did not show any improvement following the use of nimodipine in patients who were included in the study within 48 hours.\textsuperscript{8,9} However, in the American nimodipine study, post hoc analysis showed that the subgroup which had presented within 48 hours of stroke and whose initial CT was negative, showed a statistically significant improvement with 120 mg of nimodipine per day, but not in the group receiving 60 mg or 240 mg.\textsuperscript{8} No satisfactory explanation was offered for this and it was postulated that it possibly was due to the high incidence of discontinuation and deaths in the 240 mg group or as a result of statistical error despite the corrections.

Here we conclude that administration of nimodipine in the doses of 120 mg per day orally within 24 hours of stroke is definitely beneficial in the subjects suffering from mild to moderately severe stroke, as we had excluded severe or complicated subjects of stroke. Use of intravenous nimodipine has been shown to be irrevocably effective in the limitation of neurological deficit in patients of stroke.\textsuperscript{13} This study confirms that oral nimodipine is also quite effective in rapid neurological recovery after stroke. This may be significant in the developing countries, where intravenous nimodipine is not easily available and is also very expensive, oral nimodipine is a cost-effective alternative.

REFERENCES