Effects of nimodipine on cerebral hemodynamics, and prognosis of diffuse axonal injury patients

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ABSTRACT

Objectives: To evaluate the effects of nimodipine on hemodynamic state, vasospasm, and short time prognosis of diffuse axonal injury (DAI) patients.

Methods: In a prospective, clinical trial double blind study, 40 DAI patients with Glasgow coma scale of 5-8 were selected and randomly divided into 2 equal groups. The first group was treated with 60 mg of nimodipine every 4 hours immediately after admission, and the control group did not receive this treatment. Mean blood flow velocity (MFV) and pulsatility index of both middle cerebral arteries were measured using transcranial Doppler on the 1st, 3rd, and 10th days of admission. Glasgow outcome scale was evaluated one month after admission. This study was performed from June 2003 to June 2004 at Imam Medical Center, Tabriz, Iran.

Results: There were significant differences in MFV among the 3 transcranial Doppler, which demonstrated hemodynamic changes in these patients. Nimodipine did not have any significant difference on MFV between the treatment and control groups. In the nimodipine group, 45% had good prognosis (30% in the control group) and nobody had vasospasm on the 10th day Doppler study (15% in the control group), although it did not show any statistical significant difference between them.

Conclusion: Nimodipine improved the prognosis and decreased vasospasm, however, there was no statistical difference. Therefore, we suggest further studies in a larger number of DAI patients.


Diffuse axonal injury (DAI) is one of the most important traumatic brain injuries leading to impairment of consciousness and late disability. Clinically, DAI can be defined as severely impaired neurological function in patients without gross parenchymal contusions, lacerations, or hematomas. In the acute phase, DAI can be diagnosed on CT as multiple punctuate hemorrhage, typically in deep or subcortical white matter, cerebral gray-white matter interface, corpus callosum, basal ganglia, and the dorsolateral aspect of brainstem and cerebellum. Traumatic brain injury disrupts brain calcium homeostasis, leading to an increase in intracellular Ca\(^{2+}\) via voltage sensitive channels and secondary ischemic damage. How to reduce Ca\(^{2+}\) overloads and abate secondary brain damage are vital factors in the prevention of brain injury. Nimodipine, which blocks L-type voltage sensitive Ca\(^{2+}\) channels, has been shown to be protective in some models of cerebral ischemia. For traumatic and aneurysmal subarachnoid hemorrhage (SAH), nimodipine has become a standard treatment. It has been used in the treatment of head trauma, as it suppresses extra cellular calcium influx into cells and stimulates Ca\(^{2+}\) adenosine triphosphatase (ATPase) to increase Ca\(^{2+}\) efflux via calcium pumps, inhibits Ca\(^{2+}\) rise in smooth muscle cells in brain microvessels, and relieves spasm. Finally, it protects cerebral vessels from the spasm induced by agents such as noradrenaline, calmodulin, arachidonic acid, and endothelin. However, nimodipine acts on spastic vessels selectively and improves blood flow in ischemic areas. It has little effect on normal vessels, so there is no significant increase in intracranial blood volume. Therefore, it can prevent brain edema and further increase of intracranial pressure (ICP). The literature shows only a few studies assessing the effectiveness of nimodipine on DAI patients. Thus, the present investigation was designed to study hemodynamic changes in DAI patients and the effects of nimodipine on Doppler variable and the patient's outcome.

Methods. This study is a prospective clinical trial and a double blind study that assesses the effects of nimodipine on hemodynamic changes of cerebral vessels and the short time prognosis in DAI patients. This study was
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performed from June 2003 to June 2004 in the trauma ward of Imam Khomeini Medical Center of Tabriz University of Medical Sciences, Tabriz, Iran. The study was approved by the local research ethics committee. Patients of both genders, aged above 12, with Glasgow coma score (GCS) score of 5–8, with brain CT findings of DAI (multiple punctuate hemorrhage in deep or subcortical white matter, cerebral gray-white matter interface, corpus callosum, basal ganglia, dorsolateral aspect of brainstem and cerebellum) within the first 12 hours of head trauma were enrolled. In this study, exclusion criteria were as follows: a) Patients with GCS score less than 5 or more than 8, b) Patients requiring a neurological procedure during their treatment course (such as the delayed intra cranial hematoma), c) Patients with a traumatic SAH on early brain CT, d) Patients with major trauma in other organs, e) Patients who had poor temporal window to perform transcranial Doppler (TCD), f) Patients with arrhythmia due to difficulty in TCD parameter interpretation. In all patients, after intubation in the emergency unit, the brain CT scan was performed immediately. The patients were admitted to the neurosurgery intensive care unit (ICU) ward and received the same management. Forty patients were included in this trial, randomized in 2 equal groups. The first group underwent treatment with nimodipine 60 mg every 4 hours via gavage in the first 12 hours of their admission. The control group did not receive this treatment. Both groups were matched for age, gender, and GCS. All patients underwent bedside TCD studies on days one, 3, and 10 of their admission. Doppler studies were carried out using a TCD machine (D-3000 model, Medelink, France) by 2-MHZ transducer and standard protocol.9 Peak systolic velocity (PSV), end diastolic velocity (EDV), mean flow velocity (MFV), and the pulsatility index (PI) of both middle cerebral arteries (MCA) was recorded. The MFV was calculated by 2×EDV+PSV/3 and PI by PSV-EDV/MFV.9 Normal MFV in MCA is 62±12 cm/sec.9,10 We considered MFV >100 cm/sec in MCA as vasospasm.11 The PI normal value was 0.7±0.3.9 The person performing TCD was constant to minimize the bias, and blind to the treatment coding. The physician who evaluated the patients’ clinical status was blind to the patients’ subgroup and TCD results. One month later, the patients’ states were assessed with Glasgow outcome scale (GOS) system. The GOS score was considered as poor prognosis if GOS score were one (death), 2 (persistent vegetative state) or 3 (severe disability), and good prognosis if GOS score were 4 (moderate disability) or 5 (good recovery).1,12

The comparison of qualitative variables of the 2 groups was analyzed by Chi-square test. To compare Doppler variables and the effects of treatment on them, we utilized repeated ANOVA. All data were expressed as mean ± SD. The level of significance was set at p-value <0.05. The data were analyzed by SPSS statistical software.

**Results.** The study population consisted of 40 patients (32 males and 8 females) with age range of 12-70 years (28.25±14.08). The treatment group included 20 patients (16 male, 4 female) with a mean age of 26.90±12.88 and GCS of 7±1. The control group is composed of 17 male and 3 female patients, with a mean age of 29.60±15.38 and GCS of 7±1. There were no significant differences between both groups for age, gender, and GCS. The most common cause of DAI was traffic accidents (80%).

**Hemodynamic changes in MCA.** The statistical analysis of data revealed a significant difference in MFV values of the 3 TCD (p-value= 0.010 in right MCA and 0.003 in left MCA), which represents hemodynamic changes in cerebral vessels in patients with DAI. However, no significant difference in PI of MCA was detected. Nimodipine could not create a significant change of MFV and PI between the treatment and control groups (Tables 1 & 2).

**Cerebral vasospasm.** The first TCD demonstrated 5% vasospasm in the treatment group, and 25% vasospasm in the control group. The second TCD showed 5% in the treatment group and 15% in the control group, and the third TCD revealed 0% in the treatment group and 15% vasospasm in the control group. However,

| Table 1 - Changes in mean flow velocity (cm/s) in nimodipine and control groups between the 3 Doppler studies. |
|--------------------------|------------------|------------------|------------------|------------------|
| **Middle cerebral artery (MCA)** | **First TCD** | **Second TCD** | **Third TCD** | **P-values** |
| **Right MCA** Nimodipine | 63 | 69 | 56 | 0.241 |
| Control | 78 | 73 | 62 |  |
| **Left MCA** Nimodipine | 71 | 78 | 61 | 0.907 |
| Control | 70 | 94 | 60 |  |

TCD - transcranial Doppler

| Table 2 - Changes in pulsatility index in nimodipine and control groups between the 3 Doppler studies. |
|--------------------------|------------------|------------------|------------------|------------------|
| **Middle cerebral artery (MCA)** | **First TCD** | **Second TCD** | **Third TCD** | **P-values** |
| **Right MCA** Nimodipine | 0.80 | 0.86 | 0.97 | 0.183 |
| Control | 0.77 | 0.86 | 0.74 |  |
| **Left MCA** Nimodipine | 0.82 | 0.83 | 0.94 | 0.304 |
| Control | 0.78 | 0.86 | 0.75 |  |

TCD - transcranial Doppler
nimodipine could not establish a significant difference between them.

**Outcome.** For evaluating prognosis, and its relationship with nimodipine consumption, the clinical status of the patients was assessed with the GOS system. In the control group, 14 patients (70%) had poor prognosis, and 6 patients (30%) had good prognosis. However, in the nimodipine group, there was poor prognosis in 11 patients (55%), and good prognosis in 9 patients (45%). However, there was no significant difference between them \((p=0.257)\). In patients with good and poor prognosis, hemodynamic variables in MCA were compared and no significant differences were found.

**Discussion.** Diffuse axonal injury is considered the main cause of morbidity and mortality in head injury. Posttraumatic elevation of intracellular free calcium may aggravate an injury of the cellular membrane, and one of the most rewarding therapeutic options is the blockage of calcium channels. It can inhibit the post-traumatic influx of calcium ions, which activate the biochemical process resulting in secondary axotomy between 12 to 24 hours after the initial impact. Calcium entry into cells is a final common pathway in the death of nerve cells. It has been reported that the increased endothelin following head injury constricts cerebral vessels. According to some studies, the production of endothelin is calcium dependent. In rabbits treated with nimodipine, less cellular damage and less spasm of the MCA were reported. Nimodipine decreases neurological morbidity, improves the outcome, and is a safe drug. Disturbed cerebral autoregulation following head trauma has been shown to correlate with an unfavorable outcome. Cerebral autoregulation is significantly impaired during the first 2 days after head injury in patients with detrimental outcome; therefore, it should be managed intensively soon after admission.

The hemodynamic effects of nimodipine treatment can be monitored with serial TCD investigations. Arterial vasospasm and delayed ischemic deficit are considered important sequel of head trauma with unfavorable effects on outcome. In the literature, we found only one study on the effects of nimodipine on DAI patients. According to this study, which assessed 89 patients with DAI, nimodipine treated patients had shown favorable outcome 3 months after head injury. However, nimodipine could not create a significant difference between the 2 groups.

According to our results, despite the significant difference in MFV of MCAs, therapeutic interventions with nimodipine could not establish a statistically significant difference between the 2 groups. Vasospasm was 0% in the third Doppler of nimodipine receiving patients, and they had a better prognosis in comparison with the control group. Among the Doppler variables, PI and MFV of MCA are the most important. Normal PI values in this study represent normal ICP values in the DAI patients, mentioned in other studies. Simultaneous ICP monitoring is needed to confirm this finding. Although nimodipine did not induce significant change in MFV, it as a neuroprotective agent that may help the improvement of DAI patients.

In conclusion, although nimodipine tends to give a better prognosis and reduced vasospasm, it cannot create a significant statistical difference. We think that one of the most important goals in clinical management of DAI is the prevention of ischemic brain damage due to a higher incidence of cerebral vasospasm in these patients. This study had limitations in the number of patients, TCD study (only 3 times), and the follow up period (only one month). It seems that, further controlled study involving a larger number of DAI patients with more TCD study (preferably monitoring) and long term follow up are necessary for further evaluation.

**References**


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