Nimodipine can improve cerebral metabolism and outcome in patients with severe head trauma

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Abstract
In the present study, the effect of nimodipine was investigated in a patient with severe head trauma. Nimodipine was administered into the peripheral vein to prevent secondary neuronal damages in patients. The five patients in control group were treated according to the standard procedures without nimodipine. Other five patients in nimodipine group were treated with standard procedures plus nimodipine. Cerebral perfusion pressure (CPP), intracranial pressure (ICP), jugular venous oxygen saturation (SjvO2), jugular lactate and glucose levels were measured. Additionally, all patients were evaluated with Glascow outcome score (GOS) before discharge. It was found that CPP (p < 0.05) and SjvO2 (p < 0.05) were significantly higher; but, ICP (p < 0.001), jugular lactate (p < 0.05) and jugular glucose (p < 0.05) were lower in nimodipine than that of control groups. Again, GOS values were significantly higher in nimodipine than that of control groups (p < 0.05). Results of this study revealed that nimodipine can improve cerebral metabolism and outcome in patient with severe head trauma. Thus, nimodipine may be considered as a protective agent against severe head trauma related neuronal injuries.

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1. Introduction
Severe traumatic brain injury is an important public health problem with a high mortality and morbidity rate [1]. With a better understanding of the pathophysiology of traumatic brain injury, increasing effort has been applied to the development of neuroprotective measures [1,2]. It was shown that cerebral blood flow (CBF) is decreased but oxygen consumption is increased in the acute phase after severe head trauma [3–7]. Treatment of cerebral ischemia may improve outcome of these patients. Secondary mechanisms, such as excitotoxicity can increase brain edema and intracranial pressure (ICP), and decrease cerebral perfusion pressure (CPP) and brain oxygenation [3,8–12].

Some agents are used as neuroprotective against traumatic brain injuries [13]. One of them, L-type calcium channel blocking agent, nimodipine had been used clinically and experimentally and has been shown to dilate cerebral arterioles and to increase cerebral blood flow in humans and animals [1,14,15]. The neuroprotective effect of nimodipine is still not completely clear but, might be related to vasodilating, and calcium channel blocking [1,2].

The role of intracerebral lactate after head injury has been much debated recently [3,5]. It has been hypothesized that lactate constitutes the preferred substrate over glucose in neurons, especially in times of increased metabolism [3,16–20]. This is because neurons use lactate by converting it to pyruvate which then enters the mitochondrial Krebs-cycle to produce adenosine triphosphate (ATP) synthesis [3,21], as long as mitochondria are functioning [3,22].

The aim of this study is to control and prevent secondary neuronal damages by giving nimodipine in the patients with severe head trauma. Therefore, CPP, jugular venous oxygen saturation (SjvO2), jugular lactate and glucose levels were measured and Glascow outcome score (GOS) was determined in all patients.

2. Materials and methods
All patients were admitted to the neurosurgical intensive care unit, examined and evaluated by Glascow coma score (GCS). A total of 10 patients who had suffered a severe head injury, with a GCS ≤ 8 were included in the study. Diffuse brain edema was determined in computerized tomographies of all patients. The patients with
traumatic or chronic lung pathology, or brain lesion requiring surgical operation are excluded in this research. Again these patients had no pre-existing cardiovascular, hepatic, diabetic, renal or hematological conditions. There was no prescription or illicit drug use in their medical histories. The study protocol was approved by the local Ethics Committee for Human Research at Cumhuriyet University. Information consent was obtained from the families of the patients. Patients are divided into two equal groups as “control” and “nimodipine”, according to the treatments applied to them. Five patients in control are given only a standard treatment. The other five patients who put in nimodipine group are given standard treatment and nimodipine. Randomization of patients was done as follow: first patient, included in the study, was given standard treatment and nimodipine, second patient was given only standard treatment, in sequence until the whole group formed. In other words nimodipine was given to every other patient in sequence within the group.

2.1. Standard treatment procedure

All patients were ventilated mechanically, sedated with intravenous infusions of propofol (2–5 mg/[kg h]) and fentanyl (1–2 μg/[kg h]) and paralyzed with atracurium (0.5–1 mg/[kg h]). Ventilator management was tailored to maintain a PaO2 level between 95 and 100 mmHg and a PaCO2 level between 30 and 35 mmHg. All patients received dexamethasone (0.2 mg/[kg day], intravenously), ranitidine (2 mg/[kg day]), intravenously) and anti-convulsant (4 mg/kg phenytoin, by nasogastric tube). In patients with ICP values higher than 20 mmHg, a treatment is applied by giving mannitol in a dose of 1 g/kg. In patients who have very high level of ICP and mannitol is not sufficient to control, cerebrospinal fluid (CSF) drainage is also added to the treatment procedure. In these patients intra-ventricular catheters were possible to insert.

2.2. Nimodipine administration

As soon as they are taken to the intensive care, all the patients of nimodipine group were given nimodipine (Nimotop®, Bayer, Leverkusen, Germany) for a week according to the following dose and time plan; 1 mg/h in the first 2 h, and 2 mg/h for the rest of the hours.

2.3. Standard monitoring

Routine invasive monitoring of these patients included mean arterial pressure (MAP), intracranial pressure (ICP; Integra® Neurosciences, Camino, San Diego, CA, USA), cerebral perfusion pressure (CPP = MAP – ICP), central venous pressure (CVP), and continuous SjvO2 (4.5-Fr peel away introducer, 4-Fr fiber-optic catheter; Abbott pediatric pulmonary artery flotation catheter; Abbott Park, IL). Desaturations of SjvO2 of <50% were confirmed and the cause was determined by using a standard algorithm including confirmation of catheter position and calibration [13,23].

MAP, CVP, SjvO2, heart rate (HR), respiration rate (RR), arterial oxygen saturation (pulse oxymetry), and fever were observed by the intensive care monitor (Spacelabs® Medical, Inc. 90369, WA, USA) and recorded at every hour. Glucose and lactate levels in jugular blood were measured and recorded simultaneously with peripheral venous glucose (Autoanalyser Toshiba®) and lactate levels three times a day every after 8 h. Serum lactate levels were studied by using commercial kits (Spinreact) [24]. In this method, lactate was oxidized by lactate oxidase to pyruvate and hydrogen peroxide, which under the influence of peroxidase, 4-aminophenazone and 4-chlorophenol form a red quinine compound. MAP, ICP, CPP, SjvO2 saturation, jugular venous glucose and lactate levels, peripheral venous glucose and lactate levels were obtained from the patients of both groups and compared. Functional outcome was evaluated at discharge from the hospital by the GOS as follows: 1 = death, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability and 5 = good recovery [25].

2.4. Statistical analysis

Statistical analyses of data were analysed with SPSS statistical software (SPSS for Windows; Release 10.0.1 Standard Version). Comparisons between groups were performed by repeated measures analysis of variance (ANOVA) and t-test (for initial values). Categorical data (GCS, GOS) were analysed by Mann–Whitney U-test. A value of p < 0.05 was considered to be statistically significant.

3. Results

A total of 10 patients suffering from severe head injury were studied; six males and four females in average. Patients of both groups were taken to the hospital mostly after a motor vehicle accident. In all the patients, ICP sensor and internal SjvO2 probe were placed. None of the patients were treated by any type of open surgical operation.

Demographic data for the patients who were treated without nimodipine and for patients treated with nimodipine is shown in Table 1. Demographic data were similar both in groups. Initial values of HR, MAP, RR, CVP, ICP, CPP, jugular lactate, jugular glucose, SjvO2 and GCS in control and nimodipine group were presented in Table 2. Initial values of control and nimodipine groups were very close with no significant differences.

Obtained mean values, during a week observations and laboratory measurements, HR, MAP, RR, CVP, ICP, CPP, jugular lactate, jugular glucose, SjvO2 and GCS in control and nimodipine groups were presented in Table 3. We found that there were no significant differences between HR, MAP, RR and CVP values of control and nimodipine groups. ICP value was 18.15 ± 10.7 for control group.
Table 3
Mean hemodynamic, respiratory, laboratory and outcome results of control and nimodipine groups for a week.

<table>
<thead>
<tr>
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<th>Control (mean ± S.D.)</th>
<th>Nimodipine (mean ± S.D.)</th>
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<tbody>
<tr>
<td>HR</td>
<td>79.55 ± 12.5</td>
<td>84.42 ± 16.7</td>
</tr>
<tr>
<td>MAP</td>
<td>94.31 ± 14.3</td>
<td>93.45 ± 14.7</td>
</tr>
<tr>
<td>RR</td>
<td>18.54 ± 5.7</td>
<td>21.48 ± 5.1</td>
</tr>
<tr>
<td>CVP</td>
<td>5.21 ± 1.8</td>
<td>5.27 ± 1.8</td>
</tr>
<tr>
<td>ICP</td>
<td>18.15 ± 10.7</td>
<td>9.36 ± 5.4</td>
</tr>
<tr>
<td>CPP</td>
<td>76.56 ± 18.1</td>
<td>84.24 ± 14.8</td>
</tr>
<tr>
<td>SjvO2</td>
<td>67.91 ± 13.3</td>
<td>75.54 ± 9.3</td>
</tr>
<tr>
<td>Jglu</td>
<td>140.47 ± 41.6</td>
<td>121.11 ± 32.3</td>
</tr>
<tr>
<td>Pglu</td>
<td>136.27 ± 42.1</td>
<td>148.40 ± 42.7</td>
</tr>
<tr>
<td>Ilac</td>
<td>14.05 ± 6.1</td>
<td>11.51 ± 4.2</td>
</tr>
<tr>
<td>Plac</td>
<td>13.51 ± 5.2</td>
<td>12.16 ± 4.8</td>
</tr>
<tr>
<td>GOS</td>
<td>3.2 ± 1.30</td>
<td>4.8 ± 0.44</td>
</tr>
</tbody>
</table>

HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; CPP, central venous pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; SjvO2, jugular venous oxygen saturation; Jglu, jugular glucose; Pglu, peripheral glucose; Ilac, jugular lactate; Plac, peripheral lactate; GOS, Glasgow outcome score.

* p < 0.05 versus control, by ANOVA.
** p < 0.001 versus control, by ANOVA.
† p < 0.05 versus control, by Mann–Whitney U–test.

Nimodipine is a dihydropyridine-derived calcium antagonist which has been shown to dilate cerebral arterioles and to increase cerebral blood flow in human. The selectivity of the brain action of nimodipine lies in its highly lipophilic property. It easily and rapidly crosses the blood brain barrier. Thus, the regulation of the intracellular calcium homeostasis and increasing cerebral blood flow with nimodipine may be of some neuroprotective value by preventing cell death following brain ischemia [33]. The lower ICP and higher CPP values observed in patients given nimodipine compared to the ones not given in the present study suggest that nimodipine may increase cerebral blood flow, regulate the intracellular calcium homeostasis, and reduce cell swelling and death due to its neuroprotective effects.

In previous studies, hypotensive side-effect of nimodipine has been observed in some patients with subarachnoid hemorrhage (SAH) [34,35]. However, in the present study, we did not observe hypotensive effect in patients who received nimodipine. Furthermore, MAP values in both groups were very close and there was no statistical difference. Again, CPP value in nimodipine-administered group was higher than that of control. Cruz [36] have measured oxygen outcome by inserting jugular venous catheter in patients with traumatic brain damages and reported that the neurological outcome were better in patients with higher cerebral oxygen outcome than the ones with lower cerebral oxygen outcome. In this study, higher SjvO2 values were obtained in group with nimodipine compared to the group of standard control and higher SjvO2 patients presented much better neurological outcome. We believe that, this effect of nimodipine may be related to vasodilatation and increase in the brain blood flow. This result attained in this study is consistent with the literature [33,36]. Hyperglycemia is commonly seen in patients with severe traumatic brain injury, occurring in up to 87% of patients at admission to the intensive care unit [30,37]. Some studies have revealed a significant correlation between hyperglycemia and poor neurological outcome [30,37,38]. The cause of this condition is multi-factorial. The acute sympathetic system activation results in an increase in the serum catecholamin levels [30,39]. Therefore, blood glucose level rises by increasing glycogenolysis or gluconeogenesis, and inhibiting insulin secretion [30,40]. An increase in the cortisol levels
and cytokines such as interleukin-6 or brain-specific mechanisms, probably through hypothalamic involvement, also may contribute to hyperglycemia [30,41,42].

Diaz-Parejo et al. [43] have studied the effect of hyperglycemia in patients with heavy brain trauma on cerebral energy metabolism and reported that extra cellular lactate levels remarkably increased in patients with severe head trauma on cerebral energy metabolism.

GCS

6. Study limitations

Since only the patients who had severe head trauma with a GCS < 8 are included, and the ones with traumatic or chronic lung pathology or brain lesion which requires surgical operation are excluded in this research, total number of the patients for this study is not very high. Further studies with groups of larger samples would be necessary to investigate the effectiveness of this drug in detail.

References


