Comparison of Nimodipine Administration Routes in Cerebral Vasospasm After Subarachnoid Hemorrhage

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Summary

Background and purpose: Increasingly numerous studies have indicated that nimodipine can be recommended as an effective and safe agent for the treatment of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage (aSAH). However, data regarding its delivery route in the treatment of aSAH are inconsistent. The aim of this study was to assess and compare the effects of different administration routes on the functional improvement of patients with aSAH.

Methods: We retrospectively reviewed 27 patients with aSAH. Of these 27 patients, 2 had intraventricular bleeding and 10 had cerebral hematoma. All patients were divided into 3 groups as follows: the topically applied nimodipine group, the systemically applied nimodipine group and the control group. Patients were treated with nimodipine and the neurological status at discharge and at 3 months were recorded. Transcranial doppler sonography (TCD) was used to monitor cerebral vasospasm following surgical clipping. Liver function and intracranial infection were assessed among three groups.

Results: The blood flow velocity was significantly increased at days 1, 5 to days 7, 10 and day 14 after surgery in the topically applied nimodipine group. 2 out of 10 (20%) patients had intracranial infection in the topically applied nimodipine group. There were no intracranial infections in the systemically applied nimodipine group and the control group.

Conclusion: Different administration routes may affect the functional improvement in patients with aSAH. The combined use of systemically and topically applied nimodipine may be effective for treatment of cerebral vasospasm following surgical clipping of aneurysms.

Key words: Cerebral vasospasm, aneurysm, subarachnoid hemorrhage (SAH), nimodipine

Subaraknoid Kanama Sonrası Serebral Vazospazmda Nimodipinin Veriliş Yollarının Karşılaştırılması

Özet

Giriş ve amaç: Anevrizmal subaraknoid kanama (aSAK) sonrası semptomatik vazospazmın tedavisinde nimodipinin etkili ve güvenilir bir ajan olduğu giderek sayılan artan çalışmalara önerilmektedir. Ancak aSAK tedavisinde veriliş yolları ile ilgili bilgilerde çelişkiler vardır. Bu çalışmamın amacı aSAK hastalarında fonksiyonel işlevi üzerine farklı veriliş yollarının etkilerini değerlendirmek ve karşılaştırmaktır.

Yöntem: Geriye dönük olarak 27 aSAK hastası değerlendirildi. Bu 27 hastadan 2'sinde ventrikül içi kanama ve 10'unda ise serebral hematom vardı. Tüm hastalar topikal nimodipin uygulanan grup, sistemik uygulanan nimodipin grup ve kontrol grup olmak üzere 3 gruba


Yargı: Farklı nimodipin uygulama yolları aSAK hastalarında fonksiyonel düzelmeyi etkileyebilir. Sistemik ve topikal nimodipinin birlikte kullanımı anevrizmaların cerrahi kliplenmesinden sonra gözlenen vazospazmda etkili olabilir.

Anahtar Kelimeler: Serebral vazospazm; anevrizma; subaraknoid kanama (SAK), nimodipin

INTRODUCTION

Cerebral vasospasm (CVS), a reversible narrowing of the subarachnoid arteries, is one of the most considerable complications of subarachnoid hemorrhage (SAH)(3,4). CVS usually occurs due to a ruptured aneurysm or hemorrhage from arteriovenous malformation (AVM). CVS may also occur in patients who suffer SAH resulting from traumatic brain injury. Even some CVS are related to the aneurysmal treatment such as clipping or embolization(12,17). The blood accumulated in the subarachnoid space can trigger vasospasm. Endothelial dysfunction, or loss of autoregulation following SAH, may lead to decreased cerebral blood flow (CBF), which subsequently may develop into cerebral infarction(13). Although CVS is reversible, persistent CVS may lead to cerebral infarction and is associated with increased mortality and poor prognosis following SAH(1). Moreover, extensive CVS may cause delayed cerebral ischemia in approximately 20 to 40% of patients with SAH.

There is a considerable variety of management practices for CVS following SAH across high-volume centers in the world. To date, the only drug shown to be efficacious on both the incidence and poor outcome of vasospasms is nimodipine. Compared with placebo, nimodipine can significantly improve clinical outcomes, as assessed by self-formulated standards and Glasgow outcome scores, and it can significantly reduce the occurrence of symptomatic CVS and delayed neurological function deficits(14). Oral administration(14) and intra-arterial infusion(8,15) of nimodipine has been reported in clinical practice for treatment of CVS following SAH. However, there are no clinical studies investigating the comparative effects of routine treatment modalities of nimodine for patients with CVS, although a comparison of nimodipine delivery routes in CVS after SAH was reported in an experimental study with rabbits(16).

Therefore, this study was aimed to assess and compare the effects of different administration routes on the functional improvement in patients with aSAH.

MATERIAL AND METHODS

Patients

Institutional review board approval and informed consent was obtained. We retrospectively reviewed 27 patients with aSAH. The presenting symptoms were severe headaches and vomiting in 24 patients. Three patients presented with ophthalmic nerve palsy. The average age of the patients was 49 years (age range 31-82). There were 19 males and 8 females. All patients had a CT scan and SAH was noticed in all patients. aSAH was confirmed by the presence of cerebral aneurysms on computer tomography.
angiography (CTA). Of these 27 patients, 2 had intraventricular bleeding and 10 had cerebral hematoma. All patients were treated with clipping of aneurysms within 72 hours after onset of symptoms. Five patients were treated within 24 hours. Ten patients were treated between 24 to 48 hours. Twelve patients were treated within 48 to 72 hours.

All patients were divided into 3 groups as follows: the topically applied nimodipine group, the systemically applied nimodipine group and the control group. The following drugs were used: NIMOTOP® 30 mg tablets which contains 30 mg Nimodipine and NIMOTOP®IV solution that contains 10 mg/50 mL nimodipine. The topically applied nimodipine was administered as previously described(3). In brief, a drainage tube was placed at the lateral ventricle or the basal cistern and kept for 7 days. NIMOTOP®IV solution was diluted with normal saline at a ratio of 1:4 and was administered for 7 days by using a pump. The systemically applied nimodipine group was treated with the same diluted NIMOTOP®IV solution for 7 days. Patients received NIMOTOP® 30 mg tablets, given at a dose of 60 mg every 4 hours from day 7 to day 14.

Transcranial doppler sonography (TCD) evaluation

TCD was performed to monitor vasospasms on a daily basis before surgery and from day 1 to 7 after surgery. Follow-up TCD examination was performed on day 10 and 14. Blood pressure was monitored before surgery and from day 1 to 7 after surgery.

Blood pressure monitoring

Blood pressure was measured at bedside at 6 AM. The average blood pressure after surgery was compared with the blood pressure (BP) level before surgery.

Monitoring of intracranial infection

Intracranial infection was carefully observed and monitored. Intracranial infection was considered present if the patient had fever or positive meningismus and positive cerebrospinal fluid (CSF) results, suggestive of CNS infection.

Monitoring of Liver function

Liver function was monitored before surgery. The liver function was documented on a weekly basis after surgery. We evaluated alanine transaminase (ALT), aspartate aminotransferase (AST) and total bilirubin level. All patients had normal liver function before surgery. Abnormal liver function was defined as ALT or AST > 40 U/L, or total bilirubin >17.2 μmol/L.

Neurological Assessment

Neurological function was assessed at discharge and at 3 month follow up by using the Glasgow outcome scale (GOS) score. A favorable outcome consisted of a GOS score indicating good recovery (grade 5) or moderate disability (grade 4). Unfavorable outcomes were severe disability (grade 3), a vegetative state (grade 2) and death (grade 1).

Statistical Analysis

All statistical analyses were performed by using the SPSS 11.5 software package. The rank-sum test was employed to assess the neurological GPS scores among different groups. The analysis of variance (ANOVA) test was used to assess the BP and TCD results among different groups. A p value < 0.05 was considered statistically significant.

RESULTS

The neurological status of each of the three groups is listed in Table 1. There are no statistical differences among the three groups. The functional outcomes of three groups are listed in Table 2. There are no statistical differences among the three groups. There was an obvious decrease in the systolic and diastolic blood pressure after surgery in patients who received systemic nimodipine treatment (P<0.05). In contrast, the change of blood pressure
was not significant in the topically applied nimodipine group and the control group (Table 3).

The middle cerebral artery (MCA) blood flow velocity was compared among three groups before and after surgical clipping of aneurysms. In the topically applied nimodipine group, the blood flow velocity was significantly increased at days 1, 5 to 7, 10 and 14 but not days 1, 2 and 14 after surgery. In contrast, in the systemically applied nimodipine group, the blood flow velocity was found to increase from day 2 to 4 but not days 1, 5, 7, 10 and 14. In the control group, the blood flow velocity was significantly increased at days 1 to 7 and 10, but there was no obvious change at day 14.

The MCA/ICA ratio was further compared among three groups before and after surgical treatment. In the topically applied nimodipine group, the MCA/ICA ratio was significantly increased at days 3 to 7 and 10 after surgery, but there was no significant changes at days 1, 2 and 14. In the systemically applied nimodipine group, the MCA/ICA ratio was significantly increased at days 2 to 4 but not at days 1, 5 to 7, 10 and 14. In the control group, the MCA/ICA ratio was significantly increased at days 1 to 4, 6, 7 and 10 but not at days 5 and 14 after treatment.

Liver function was also assessed among three groups. Three out of seven (42.86%) patients had abnormal liver function in the systemically applied nimodipine group. There was no incidence of liver function impairment in the topically applied nimodipine group and the control group. Incidence of intracranial infection was compared among three groups. In the topically applied nimodipine group, 2 out of 10 (20%) patients had intracranial infection. There was no incidence of intracranial infection in the systemically applied nimodipine group and the control group.

### Table 1 Neurological status of patients with subarachnoid hemorrhage (SAH) following different nimodipine administration

<table>
<thead>
<tr>
<th>Group</th>
<th>Good</th>
<th>Mild disabled</th>
<th>Severe Disabled</th>
<th>Disabled</th>
<th>death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Systemic</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>27</td>
</tr>
</tbody>
</table>

*P*=0.3071
### Table 2 Glasgow outcome scale (GOS) score in patients with subarachnoid hemorrhage (SAH) following different nimodipine administration

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Systemic</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>23</td>
<td>27</td>
</tr>
</tbody>
</table>

P = 0.1408

### Table 3 The blood pressure in patients with subarachnoid hemorrhage (SAH) following different nimodipine administration (x ±s)

<table>
<thead>
<tr>
<th>BP</th>
<th>Topical group</th>
<th>Systemic group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>149.0±34.8</td>
<td>129.2±17.2</td>
<td>153.9±22.4</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>90.0±14.1</td>
<td>84.5±13.8</td>
<td>89.4±10.1</td>
</tr>
</tbody>
</table>

*P<0.05

### DISCUSSION

Rupture of a cerebral aneurysm is the most common cause of non-traumatic subarachnoid hemorrhage\(^{19}\). Aneurysmal subarachnoid hemorrhage (aSAH) accounts for about 6 to 8% of all cerebrovascular accidents, which involves 10 out of 100,000 people each year. Despite effective treatment of the aneurysm by surgical clipping or endovascular coiling, cerebral vasospasm (CVS) is still a common complication after SAH. Vasospasm is observed angiographically after three days following aneurysmal rupture\(^{15,16,19}\). The vasospasm is maximally around 1 week following rupture and usually subsides by two or three weeks. To date, the exact etiology of vasospasm is still poorly understood.

Increasing numerous studies have indicated that many factors have been involved in the pathogenesis of CVS, such as endothelial dysfunction, autoregulation deficit, and an hypovolemic component leading to a decrease in cerebral blood flow (CBF)\(^{7,10,22}\). Moreover, the red blood cell debris and endothelin-1 are proposed to be mediators of the vasospasm.

CVS is classified as either angiographic or symptomatic. Angiographic vasospasm, which is defined as arterial narrowing compared with the parent vessels, occurs in more than half of all patients and is recognized as the main cause of delayed cerebral ischemia after an event. Although digital subtraction angiography (DSA) is a
gold standard for evaluation of CVS, the invasive nature of the procedure has limited its use in clinical practice. TCD is a noninvasive imaging method that allows real-time monitoring of CVS\(^5\). Vasospasm diagnosis and monitoring is the first clinical application of TCD, and TCD is now routinely used to monitor vasospasm in many hospitals. As the caliber of major conducting arteries is reduced, the velocity of blood going through them generally increases. Patients who developed vasospasm often have an increase of mean velocities in the middle cerebral arteries. The blood flow velocity (VBF) was determined by the quantity (Q) of cerebral blood flow and the cerebral vessel diameter (D). The following formula was used to calculate the blood flow: 
\[
V_{BF} = \frac{4Q}{D^2}
\]
In the present study, the vasospasm was assessed by TCD by an experienced technician. The results indicate that topically or systemically applied nimodipine may alleviate vasospasm in patients with aSAH.

The treatment of CVS comprises hemodynamic management and endovascular procedures. Nimodipine is a voltage-gated calcium channel antagonist that acts by inhibition of calcium entry into smooth muscle cells and neurons\(^6,9,11\). Nimodipine binds specifically to L-type voltage-gated calcium channels. Its lipophilic properties allow it to cross the hematocerebral barrier. Although the exact mechanism of preventing and limiting the extension of ischemic lesions remains unknown, several studies suggested that nimodipine has been shown to attenuate the neuronal calcium increase after cellular ischemia, and cause cell death\(^2,20,23\). It was well established that the contraction of cerebral arterial smooth muscle cells was dependent on the entry of calcium ions into the cells. Nimodipine crosses the blood-brain barrier and blocks the influx of extracellular calcium. Nimodipine selectively increases CBF and reverses the CVS without altering the cerebral oxidative metabolism.

The route of administration may have an impact on the efficacy of nimodipine for treatment of CVS. Infusing intraarterial nimodipine in patients with symptomatic vasospasm has been previously reported\(^18,21\). Oral and intravenous nimodipine has been widely used for treating CVS to achieve these effects\(^18,21\). Intravenous administration of nimodipine may be associated with few minor complications such as hypotension or arrhythmia. In the present study, different administration methods of nimodipine on the functional outcomes in patients with CVS were assessed. The results indicated that the topically and systemically applied nimodipine is equally effective for treatment of CVS. There was an increase in the MCA blood flow velocity 1 to 2 days after clipping of cerebral aneurysms. Topically applied nimodipine may act on the cerebral blood vessels. There was a dramatic increase in the blood velocities 3 to 7 days after surgical clipping of aneurysms. This might be explained by the fact that the dose of the nimodipine was not sufficient enough to control vasospasm. Further studies are required to elucidate the effective dose of topically applied nimodipine in the basal cisterns.

In the present study, 2 cases of cerebral infection occurred at days 4 and 5 after aneurysm clipping in the topically applied nimodipine group. This might have been due to the prolonged placement of the drainage tube. Therefore, the drainage tube should be removed as early as possible to prevent infections. In addition, the present study showed that the time of action was faster in the topically applied nimodipine group than that in the systemically applied nimodipine group. The indicated results suggest that the nimodipine may be effective for treatment of vasospasm 5 days after surgical clipping. The combined use of systemically and topically applied nimodipine may be effective for treatment of and CVS following surgical clipping of aneurysms.
CONCLUSION

Different administration routes may affect the functional improvement in patients with aSAH. The combined use of systemically and topically applied nimodipine may be effective for treatment of cerebral vasospasm following surgical clipping of aneurysms.

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REFERENCES


