Transcranial Doppler Pattern after Intracarotid Papaverine and Prostaglandin E₁ Incorporated in Lipid Microsphere in Patients with Vasospasm

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Abstract

We studied the effects of intracarotid papaverine and prostaglandin E₁ incorporated in lipid microsphere (Lipo-PGE₁) in relation with transcranial Doppler parameters such as mean flow velocity (MFV) and pulsatile index (PI) of the proximal segment of the middle cerebral artery. Eighty patients with subarachnoid hemorrhage (SAH) were included in this study. In the case of angiographic vasospasm, papaverine at 7 mg/min with total dose below 300 mg per artery and 10–20 μg of Lipo-PGE₁ were injected in the supraclinoid portion of the internal carotid artery. Vasospasm was improved in 24 patients (63%), however, it was unchanged in 14 patients (37%). The former patients had more favorable outcomes than the latter patients (p < 0.005). After intracarotid injection therapy, the correlation between MFV and PI was classified into three types: type 1, both MFV and PI decreased; type 2, MFV decreased but PI increased; and type 3, both MFV and PI fluctuated. The Glasgow Outcome Scale 3 months after SAH was as follows: type 1 (n = 15), good in 14 (93%) and moderate disability in one (7%); type 2 (n = 9), good in eight (89%) and vegetative state in one (11%); and type 3 (n = 14), moderate disability in five (36%), severe disability in seven (50%), and death in two (14%). Chi-square analysis showed significant differences between type 1 and type 3 (p < 0.005), and type 2 and type 3 (p < 0.005). In conclusion, intracarotid papaverine combined with Lipo-PGE₁ was effective for vasospasm but type 3 patients require a different treatment protocol.

Key words: transcranial Doppler, subarachnoid hemorrhage, vasospasm, papaverine, prostaglandin E₁ incorporated in lipid microsphere

Introduction

The development of transcranial Doppler ultrasonography (TCD) has facilitated noninvasive measurement of erythrocyte velocities in the large, basal intracranial arteries and is of clinical value in the diagnosis of vasospasm in the middle cerebral artery (MCA). However, recent studies demonstrated a lack of correlation between blood velocity as measured by TCD and neurological deficits, and elevated blood velocity as measured by TCD was not associated with ischemia. On the other hand, chronological monitoring of mean flow velocity (MFV) enabled accurate demonstration of the occurrence of vasospasm. Recently, intraarterial papaverine therapy has been widely introduced for the treatment of vasospasm. However, we are unaware of any previous study chronologically monitoring both MFV and pulsatile index (PI) after intraarterial injection therapy. In the present study, we evaluated the relationship between MFV and PI after subarachnoid hemorrhage (SAH) and the effects of papaverine and prostaglandin E₁ incorporated in lipid microsphere (Lipo-PGE₁) on vasospasm.

Materials and Methods

We studied 80 consecutive patients with SAH. Serial TCD measurements of MFV and PI of the MCA were performed using a 2-MHz pulsed Doppler probe (8500GP; Hewlett Packard, Palo Alto, Calif., U.S.A.) via the transtemporal windows, using the method described by Aaslid et al. All patients had a cisternal lavage from day 1. We used a MFV value of >120 cm/sec and/or daily increase >30 cm/sec as the criterion for vasospasm. The patients with vasospasm were subjected to cerebral angiography.
and if any narrowing was found on angiography, papaverine at 7 mg/min with total dose below 300 mg and 10-20 µg of Lipo-PGE₁ were injected in the supraclinoid portion of the internal carotid artery. Statistical analysis was performed by means of chi-square test.

**Results**

Vasospasm occurred in 38 patients (48%), of whom 30 were symptomatic (38%) and eight were asymptomatic (10%). When the effects of intracarotid injection were compared among the patients, there was a statistically significant difference in the Glasgow Outcome Scale (GOS) 3 months after SAH between dilated (n = 24) and non-dilated (n = 14) groups (p < 0.005) (Table 1). The dilated group had more favorable outcomes than the non-dilated group (Table 1).

After the intracarotid injection therapy, the correlation between MFV and PI was classified into three types: type 1, both MFV and PI decreased (clockwise change); type 2, MFV decreased but PI increased (counterclockwise change); and type 3, both MFV and PI fluctuated (Fig. 1). In each type classified by TCD parameters, GOS was as follows: type 1 (n =

<table>
<thead>
<tr>
<th>GOS</th>
<th>Dilated (n = 24)</th>
<th>Non-dilated (n = 14)</th>
</tr>
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<tbody>
<tr>
<td>Good</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Severe disability</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Vegetative state</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Significant difference between dilated and non-dilated groups (chi-square analysis, p < 0.005).

**Fig. 1** Representative relationship between mean flow velocity (MFV) and pulsatile index (PI) in each type. Prespasm: MFV and PI on the day of operation, IA: intracarotid injection of papaverine and prostaglandin E₁, incorporated in lipid microsphere, Recovery: recovery from vasospasm, Final: final status of MFV and PI.
Table 2  Correlation between Glasgow Outcome Scale (GOS) and transcranial Doppler types

<table>
<thead>
<tr>
<th>GOS</th>
<th>Type 1 (n = 15)</th>
<th>Type 2 (n = 9)</th>
<th>Type 3 (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>14</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Severe disability</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Vegetative state</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Significant difference between type 1 and type 3 (chi-square analysis, p < 0.005) and type 2 and type 3 (chi-square analysis, p < 0.005).

Discussion

In the present study, intracarotid injections of papaverine and Lipo-PGE₁ were effective in 63% of patients with vasospasm. On the other hand, vasospasm was refractory in 37% of patients. We administered papaverine at 7 mg/min with total dose below 300 mg per artery, because unexpected complications have been reported in the SAH patients after intraarterial injections of papaverine.²,¹⁶,¹⁷) Most of them are due to excessive vasodilatation and vasospasm following high dosage papaverine injections. Severe thrombocytopenia following intraarterial papaverine was also reported,¹⁷) although rare. However, the optimal dosage of papaverine for the treatment of vasospasm remains unknown. From our experience, the injection rate at 7 mg/min and total dose below 300 mg per artery seemed safe compared to the previous studies.²,¹⁰,¹¹) To enhance the vasodilatory effects of relatively lower dosage of papaverine, we first used Lipo-PGE₁ in conjunction with papaverine injections. Lipo-PGE₁ has antithrombogenic effects and causes vasodilatation in injured arterial walls.¹⁸) In addition, Lipo-PGE₁ is accumulated in lesions in vascular diseases.¹⁸) If this is the case in cerebral arteries, Lipo-PGE₁ may be beneficial for the treatment of vasospasm. Sasaki et al.¹⁹) reported endothelial disruption following experimental SAH. Therefore, Lipo-PGE₁ is expected to accumulate in injured cerebral endothelium and protect against thrombogenesis and vasospasm.

An increase in TCD velocity in the basal cerebral vessels occurs in nearly all patients after SAH,²⁰) and a rapid rise to high levels is frequently associated with clinical deterioration caused by delayed ischemia.¹,⁵,⁶,⁹,¹²,²⁰) Although the MFV cannot be translated easily into volume blood flow,¹³) additional information on cerebral hemodynamics may be derived from TCD pulsatility.⁴,⁷,⁸) The PI may be influenced by many different factors, such as heart rate, blood pressure, vascular compliance, arterial CO₂ and O₂ blood tensions, and, in the case of brain vessels, tissue compliance.⁸) When cerebral perfusion pressure (CPP) is stable, changes in PI reflect changes in cerebrovascular resistance (CVR).⁴) In such cases, a rise in distal resistance increases PI, and a rise in proximal resistance decreases PI. However, when CPP decreases, the decrease in CVR is followed by an increase in pulsatility, which may be explained by a combined change in vascular resistance and compliance of large cerebral arteries.⁴) In severe SAH cases, CPP should decrease due to intracranial hypertension. After injection therapy, PI is expected to increase for such cases (type 2). However, if CPP is maintained at a normal level, PI may decrease after injection therapy (type 1). In addition, the increase in PI is followed by an increase in compliance of large cerebral arteries.⁴) After injection therapy, a generalized relaxation of arterial smooth muscles occurs. This may mask the effect of distal vasodilatation, producing a net increase in PI. The interpretation of velocity changes in type 3 is by no means straightforward. In addition to vasospasm, many confounding factors may play a role in the steadiness of TCD parameters.

In conclusion, intracarotid papaverine combined with Lipo-PGE₁ may be a safe and effective treatment of vasospasm after SAH. However, the type 3 patients require a different treatment protocol.

References

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