The Role of Adjuvant Vinpocetine Therapy in Aspirin-Treated Cerebrovascular Patients

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ABSTRACT

BACKGROUND: The aim of our pilot study was to investigate the endothel dysfunction, hemorheological and agonist-induced platelet aggregation changes in aspirin-treated cerebrovascular patients after parenteral vinpocetine admission (VP).

METHODS: Hemorheological parameters (hematocrit, plasma fibrinogen, whole blood viscosity, red blood cell aggregation and deformability), endothel dysfunction markers (von Willebrand factor, soluble P-selectin) and agonist-induced (collagen, epineprine, arachidonic acid and adenosine-diphosphate) platelet aggregation values were evaluated at baseline, 7th and 30th day.

RESULTS: Parenteral vinpocetine infusion significantly decreased von Willebrand factor levels and arachidonic acid-induced platelet aggregation values and they still remained significant after 30 days. Red blood cell deformability was significantly decreased after a month. No statistical differences among the other examined hemorheological parameters could be found.

CONCLUSION: Vinpocetine, partially by its beneficial hemorheological and endothel-dysfunction improving profile may help to overcome aspirin resistance.

Key words: Vinpocetine; Aspirin; Antiplatelet resistance; Hemorheology; Endothelial dysfunction; Stroke

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INTRODUCTION

Cerebrovascular diseases include a group of brain disorders with ischaemic and haemorrhagic of origin and are the second leading cause of death worldwide[1]. Furthermore, these diseases are the leading cause of disability in adults[2]. However, with the exception of systemic thrombolysis and thrombectomy in hyperacute and aspirin in acute stroke syndromes, other treatment strategies have very limited efficacy[3].

Randomized, multicentre trials and meta analysis have shown the efficacy of aspirin in both the primary and secondary prevention of vascular diseases[7]. Increasing number of reports about antiplatelet (and aspirin) resistance and unfavourable clinical outcome has led to a growing concern among clinicians and patients about the efficacy of aspirin treatment[10].

Vinpocetine [ethylapovincaminate], is a derivative of the Vinca minor alkaloid vincamine, originally was developed in Hungary[9].
Vinpocetine is still widely used in the treatment of various disease states of cerebrovascular origin and its mechanisms of action are under intensive research[6,7]. The drug is claimed to be a neuroprotectant, increasing cerebral perfusion and oxygen extraction and has been shown to have beneficial hemorheological and antiplatelet properties[8,9].

Hemorheological factors are significant determinants of the flow characteristics of blood[9,10]. Several studies have proved that elevated hematocrit [Hct], plasma fibrinogen concentration, plasma and whole blood viscosity (WBV), and increased red blood cell (RBC) aggregation were independent risk factors of ischemic vascular diseases based on prevention trials[6,7]. Interestingly, hemorheological disturbances may occur in nearly half of patients with ischemic stroke (IS) [6,9]. Based on our previous results impaired rheological parameters have been shown to be associated with aspirin resistance[9,10].

The aim of our present study was to detect the beneficial effects of adjuvant vinpocetine therapy on the hemorheological parameters, endothel dysfunction and platelet aggregation values of aspirin-treated cerebrovascular patients.

**ETHICS STATEMENT**

Written informed consent was obtained from all participants. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Regional Ethical Committee at the Faculty of Medicine, University of Pécs.

**PATIENTS AND METHODS**

Twenty ischaemic chronic cerebrovascular patients took part in our present study (mean age: 60±7 years). Inclusion and exclusion criteria have been published previously[5].

Hemorheological and endothel dysfunction parameters, platelet aggregation values were determined at screening, before (visit 1) and after (visit 2 at day 7) parental admission and 30 days later (follow-up visit).

**Hemorheological measurements**

Blood samples were taken from the cubital vein; routine blood chemistry and hemorheological parameters – hematocrit, plasma fibrinogen level, plasma and whole blood viscosity, RBC aggregation and deformability – were determined. Methodology has been previously published[6,7].

### Endothel dysfunction markers

A quantitative direct enzyme immunoassay (Shield Diagnostics Ltd., U.K.) was used for the detection of von Willebrand factor (vWF) activity in human citrated plasma.

Determination of the level of sP-selectin was performed by using a sandwich ELISA procedure according to manufacturer’s instructions (Bender MedSystems, Austria). Methodology has been previously published[6,7].

### Platelet aggregation values

Epinephrine (adrenaline)-, adenosine diphosphate (ADP)-, arachidonic acid- and collagen-induced aggregation of platelets were analysed as in previous studies conducted by our workgroup[7].

### RESULTS

20 cerebrovascular patients took part in our study. High-dose parental vinpocetine infusion significantly decreased von Willebrand factor levels measuring at day 7 (1.649 ± 0.198 NU/ml vs. 1.558 ± 0.140 NU/ml, p = 0.011) and it still remained significant after a months (1.649 ± 0.198 NU/ml vs. 1.509 ± 0.126 NU/ml, p=0.001) (Table 1). Red blood cell deformability (0.563 ± 0.1 vs 0.558 ± 0.008, p=0.036) was significantly decreased at day 30 (Table 1, Figure 1). Arachidonic acid-induced platelet aggregation values were significantly decreased at day 7 (32.47 ± 7.28% vs. 21.89 ± 6.84%, p = 0.001) and day 30 (and 32.47 ± 7.28% vs. 24.56 ± 7.79% p = 0.05) (Table 1, Figure 1). There were no statistical differences among the other examined hemorheological parameters.

### DISCUSSION

Platelets have an important role in the development of atherothrombosis and subsequent vascular events. Therefore antiplatelet therapy is one of the cornerstones of both primary and secondary prevention.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (before infusion)</th>
<th>7th day (after infusion)</th>
<th>follow-up (30th day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma fibrinogen (g/l)</td>
<td>3.590 ± 0.666</td>
<td>3.591 ± 0.834</td>
<td>3.605 ± 0.680</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>43.150 ± 3.815</td>
<td>42.667 ± 4.899</td>
<td>42.555 ± 4.273</td>
</tr>
<tr>
<td>Erythrocyte aggregation (%)</td>
<td>69.584 ± 5.137</td>
<td>69.043 ± 5.323</td>
<td>69.958 ± 5.031</td>
</tr>
<tr>
<td>Erythrocyte deformability (NU/ml)</td>
<td>0.563 ± 0.010</td>
<td>0.562 ± 0.007</td>
<td>0.558 ± 0.008*</td>
</tr>
<tr>
<td>Full blood viscosity (mPa/s)</td>
<td>4.144 ± 0.457</td>
<td>4.432 ± 1.433</td>
<td>4.137 ± 0.642</td>
</tr>
<tr>
<td>Plasma viscosity (mPa/s)</td>
<td>1.254 ± 0.060</td>
<td>1.252 ± 0.085</td>
<td>1.263 ± 0.072</td>
</tr>
<tr>
<td>soluble P-selectin concentration (ng/ml)</td>
<td>2.515 ± 0.210</td>
<td>2.761 ± 0.252</td>
<td>2.558 ± 0.256</td>
</tr>
<tr>
<td>von-Willebrand factor (NU/ml)</td>
<td>1.649 ± 0.198</td>
<td>1.558 ± 0.140*</td>
<td>1.509 ± 0.126**</td>
</tr>
<tr>
<td>Collagen 2 ng/ml (%)</td>
<td>11.00 ± 10.05</td>
<td>14.10 ± 11.72</td>
<td>11.47 ± 11.85</td>
</tr>
<tr>
<td>Epinephrine 10 μM (%)</td>
<td>19.37 ± 17.33</td>
<td>17.72 ± 19.38</td>
<td>19.21 ± 8.98</td>
</tr>
<tr>
<td>ADP 5 μM (%)</td>
<td>39.79 ± 12.95</td>
<td>39.79 ± 17.41</td>
<td>33.84 ± 16.56</td>
</tr>
<tr>
<td>Arachidonic acid 500 μM (%)</td>
<td>32.47 ± 7.28</td>
<td>21.89 ± 6.84*</td>
<td>24.56 ± 7.79*</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.
Numerous patients will experience a recurrent atherothrombotic vascular event despite adequate antiplatelet therapy\(^2\)-\(^4\).

The clinical efficacy of aspirin in decreasing vascular events has been well established in the past 30 years. Despite of its regular intake, a number of atherothrombotic events still occur, raising the possibility of resistance to aspirin\(^2\)-\(^6\). In recent years, a number of reports in the medical literature have shown possible relationships between residual platelet reactivity measured by different laboratory methods and unfavourable clinical outcomes\(^7\)-\(^9\).

An exact definition of “resistance” to antiplatelet therapy on the basis of physiology does not exist\(^1\)-\(^3\). Our definition (using collagen and epinephrine) has been validated and shown in recent articles and has been associated with worse clinical outcome\(^7\),\(^10\). On the other hand, recent European consensus papers suggest the use of arachidonic acid as the most appropriate agonist in the measurement of platelet’s response to aspirin, so we also used this agent\(^11\),\(^12\).

In our study, after one week of parenteral vinpocetine infusion a significant decrease of von Willebrand factor levels could be found suggesting the beneficial effects of this drug on endothel dysfunction, which plays an important role in the activation of platelets\(^13\). Red blood cell deformability has also been significantly decreased at the 30th day also underlining this phenomena.

Mechanical stress provoked by inflammatory conditions (such as atherosclerosis) leads to an increase in the calcium (Ca) entry into erythrocyte leading to reduction in deformability with subsequent elevation in the blood viscosity. Based on previous results, vinpocetine inhibits natrium (Na)-dependent Ca-channels at erythrocyte membrane enhancing deformability and moreover, deformability was also linked via stimulation of cGMP pathway which has been shown to be augmented by vinpocetine\(^14\).

We previously showed the association between impaired hemorheological parameters and aspirin resistance\(^15\). Biochemical researches have shown decreased red blood cell deformability to be associated with increased fragility with consequent adherence and ATP release, which is a potential agonist of platelet aggregation. Red blood cells with decreased deformability migrate in the center of blood flow displacing other cells (including platelets) in small vessels, enhancing their contact to the endothelial surface\(^16\),\(^17\). Platelets from aspirin-resistant patients seem to be more sensitive and activable by ADP. This hypersensitivity can promote resistance to aspirin, raising the possibility of therapeutic improvement with other antiplatelet agents (especially clopidogrel)\(^18\). The beneficial hemorheological profile of vinpocetine may help to overcome decreased platelets’ response to aspirin and other antiplatelet agents.

The parenteral use of vinpocetine also significantly decreased arachidonic acid-induced platelet aggregation, which os the most sensitive agonist in the measurement of platelets’ response to aspirin\(^19\). In our previous work aspirin resistance was associated with unfavourable outcome in cerebrovascular patients\(^20\). Although resistance to aspirin was not an independent risk factor of future vascular events, it was a phenomena of global cardiovascular risk suggesting the use of aggressive secondary prevention strategies. The use of intensive statin treatment has recently shown to overcome aspirin resistance, maybe by its pleiotrophic effects\(^21\),\(^22\). On the other hand, our work is the first suggesting the beneficial effects of vinpocetine treatment of platelet aggregation values in aspirin-treated patients. Vinpocetine inhibits Ca\(^{2+}\)/calmodulin-dependent phosphodiesterase (PDE) type 1\(^23\). This effect would theoretically lead to an increase of cyclic AMP over cyclic GMP and may be responsible for the benefits in cerebral circulation and decreased platelet aggregation observed after vinpocetine administration\(^24\).

In conclusion, the short-term use of parenteral vinpocetine was associated with the improvement of endothel function, red blood cell deformability and platelets’ response to aspirin using arachidonic-acid induced aggregation. Preclinical and clinical studies suggested multiple effects of vinpocetine such as selective increase of cerebral microcirculation, reduction of plasma viscosity, increase of red blood cell deformability, increase of cerebral oxygen and glucose uptake and neuroprotection. Although the exact biochemical mechanism are still not known and under intensive research, our work suggesting the beneficial effects of vinpocetine treatment on aspirin resistance.

REFERENCES

