Double-Blind Controlled Trial of the Therapeutic Effects of Prostacyclin In Patients With Completed Ischaemic Stroke

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SUMMARY In a pilot study, 26 patients with acute completed strokes (48 hours to 5 days after cerebral infarction) were randomly assigned to the prostacyclin (PGI2) or placebo groups. PGI2 sodium salt (Epoprostenol, Wellcome Research Laboratories and Upjohn Company) or its solvent (glycine buffer) were infused into the subclavian vein for six-hour periods in five courses separated by six-hour intervals. Prostacyclin was administered at a rate of 2.5-5.0 ng/kg/min. A significant alleviation of neurological deficits occurred 6 and 54 hours after the treatment in patients receiving prostacyclin. This improvement lost its statistical significance at the end of a two-week observation period. It is concluded that further modified controlled studies are required to evaluate the therapeutic usefulness of PGI2 in the treatment of patients with cerebral ischaemia.

NO AVAILABLE THERAPY, including anticoagulation and thrombolytic therapy, is effective in reversing neurological impairment with completed strokes. Conversely, strokes following transient ischaemic attacks (TIA) or stroke recurrence after minor strokes can be reduced with the platelet supressant drug, aspirin. This suggests that antiplatelet therapy is effective in preventing strokes and may similarly be effective in acute ischaemic strokes.1-3 Prostacyclin (PGI2) is the most potent platelet-suppressant known.4 Its use has been successful in treating acute thromboembolic episodes, in patients with central retinal vein occlusion,5 as well as in patients with chronic peripheral vascular disease.6-10 Apart from the platelet-suppressant action, PGI2 has also vasodilatory6-9 and fibrinolytic11 properties. Specifically, PGI2 prevents impairment of post-ischaemic brain reperfusion12 and promotes postischaemic electrical recovery of cerebral neurons in dogs.13 We recently reported the beneficial effects of PGI2 therapy in ten patients with completed ischaemic stroke.14 The present controlled pilot study was precipitated by the results of this open clinical trial.14

Patients and Methods

Patients

Patients with completed ischaemic stroke attending our Neurological Department from November 1982 to August 1983, were included in this pilot trial. Ischaemic stroke in the territory of the internal carotid artery was diagnosed on the basis of a sudden onset of focal signs as evidenced by clinical and EEG examination. Intracranial hemorrhage was ruled out following CSF examination, and TIA's whose symptoms persisted beyond 24 hours were also eliminated. Patients with:

- only slightly neurological deficit (less than 10 scores),
- cardiac failure or severe arrhythmias, blood glucose level higher than 10 mmoles/l or blood urea higher than 12 mmoles/l, and body temperature higher than 37.5°C did not qualify. Furthermore, patients with neurological deficit resulting from previous stroke or those who declined inclusion in the study were not entered.

Drugs and Methods

Prostacyclin sodium salt (Epoprostenol, Wellcome Research Laboratories, U.K., and Upjohn Company, U.S.A.) or its solvent, (0.1 M glycine buffer, pH 10.5) were infused into a subclavian vein in 26 patients who were randomly assigned to the PGI2 or placebo (PL) groups. EDG was monitored continuously during infusion and arterial blood pressure measured at 30 minute intervals. The rate of infusion was 20-40 μl/min and the dose of PGI2 was at a range of 2.5 to 5.0 ng/kg/min, depending on the patient's tolerance. This dosage produced platelet suppressant action resulting in slight hypotension in man.9,14 Five consecutive infusions lasting 6 hours each were separated by 6 hour intervals. The first infusion was given not earlier than 48 hours and not later than 5 days after the occurrence of stroke. To avoid pharmacological interference with the endogenous prostanoid system, patients were not administered aspirin or other cyclooxygenase inhibitors, glucocorticosteroids, methylxanthines, dextran, nicotinic acid derivatives or furosemide. However, patients did receive general care ensuring adequate hydration, electrolytes, and nutrients. In addition, appropriate medical attention was given as needed to infections and other conditions unrelated to cerebral pathology. All patients received individually modified physical and speech rehabilitation.

Neurological Status and Assessment

Two neurologists independently assessed the neurological status of patients at T0 — immediately before the first infusion, T1 — after the first infusion was over (6 hrs), T2 — at the end of the treatment (54 hrs), and
**TABLE 1**

<table>
<thead>
<tr>
<th>Neurological Status Scoring</th>
<th>Placebo group</th>
<th>PG\textsubscript{I} group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness</td>
<td>0—15</td>
<td>0—15</td>
</tr>
<tr>
<td>Aphasia</td>
<td>0—15</td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>(0—10) × 2*</td>
<td></td>
</tr>
<tr>
<td>Disturbances of sensation</td>
<td>0—5</td>
<td></td>
</tr>
<tr>
<td>Face and tongue paresis</td>
<td>0—5</td>
<td></td>
</tr>
<tr>
<td>Homonymous hemianopia</td>
<td>0—4</td>
<td></td>
</tr>
<tr>
<td>Gaze deviation</td>
<td>0—4</td>
<td></td>
</tr>
<tr>
<td>Sphincter disorders</td>
<td>0—6</td>
<td></td>
</tr>
</tbody>
</table>

\*Separately for upper and low extremity.

Consciousness — 2 weeks after the onset of the treatment. The first three symptoms were scored with a difference of not more than 2 scores by two independent assessors. Scoring for the remaining symptoms differed by not more than 1 score (table 1). The mean of those numerical assessments by two observers was used for further statistical analysis. The observers did not see patients during the course of infusion and they were unaware of the kind of treatment administered. The general neurological status of patients was assessed by summing the scores which were ascribed to each neurological deficit according to the scale presented in table 1. The frequency of occurrence of each neurological deficit in patients of PG\textsubscript{I} and placebo groups is shown in table 2. The neurological status scoring was adopted and modified from the systems of Mathew et al\textsuperscript{15} and Martin et al.\textsuperscript{16} The graduation of each neurological deficit was standardized in the pre-prepared charts which were used by the observers. Higher score indicated a more severe deficit. A pharmacologist decoded the results at the end of the trial.

**Analysis**

The analysis was performed by both parametric and non-parametric tests in parallel. Since no correlation was found between absolute values of scores and their differences, we were allowed to use the Student’s t-test for the analysis of matched pairs. In addition, for the analysis inside the groups (table 3) the Wilcoxon matched-pair signed-rank test was used. In the case of the analysis of differences between placebo vs prostacyclin groups (table 4), apart from the Student’s t-test the Mann-Whitney U-test was used for non-parametric analysis.

**Results**

Table 2 shows relevant clinical data from 26 patients with ischaemic stroke who entered this study. There were no deaths and withdrawals were not necessary during the two-week period of observation. This could be attributed to the exclusion measures at the entrance (see Patients and Methods). Pneumonia or thrombo-phlebitis developed in 2 in both the PL group and the PG\textsubscript{I} group. One patient in the PG\textsubscript{I} group developed a phlebitis developed in 2 in both the PL group and the PG\textsubscript{I} group. On the other hand, no deaths and withdrawals were not necessary to the infusion of PG\textsubscript{I}, with marked hypertension (from 170/130 mm Hg to 270/160 mm Hg). This paradoxical hypertensive effect of prostacyclin in some patients with stroke was also observed in our open clinical trial.\textsuperscript{14} This observation remains unexplained.

Figure 1 presents the scores which were attributed to each patient in the PL and PG\textsubscript{I} groups. Most patients of both groups were initially scored between 15 and 25. High initial scoring (29—41 scores) was recorded in 2 PL and in 4 PG\textsubscript{I} patients.

Table 3 contains the statistical analysis of the data shown in figure 2 for each group of patients, separately. No significant improvement occurred at any time in the PL group. On the other hand, improvement in neurological status of the patients in the PG\textsubscript{I} group was significant at all times. This significance, however, seemed to weaken at T0—T3, in contrast to the rising difference in scores.

Table 4 presents the final statistical assessment of the net therapeutic effect of prostacyclin vs placebo in this study. Both in parametric and non-parametric tests at T0—T1 and T0—T2, there was observed a statistically significant improvement in the neurological status of
patients who were treated with PGI₂, whereas T₀—T₃, this significance disappeared. When analyzing the components of the therapeutic effects of prostacyclin vs placebo at T₀—T₁ and T₀—T₂, it became obvious that alleviation of aphasia and hemiparesis were mainly responsible for the therapeutic effects (fig. 2). Out of 8 scored neurological symptoms (table 1) 4 symptoms (disturbed consciousness, homonymous hemianopia, gaze deviation and sphincter disorders) occurred at a low frequency of 0–3 per group of patients (table 2) and therefore could not be analyzed in figure 2.

**Discussion**

In this controlled pilot study the prostacyclin treatment of patients with ischaemic stroke resulted in improvement in their neurological deficit. Alleviation of aphasia and hemiparesis mainly contributed to this beneficial effect of prostacyclin. However, the above improvement remained significant only during the course of treatment with prostacyclin and lost its statistical significance at the end of a two-week period of observation. The frequency (but not severity) of the scored symptoms was uniformly distributed between the PGI₂ and PL groups. The frequency of scored symptoms diminished in the following order: face and tongue paresis, hemiparesis, sensor disturbances, and aphasia, and varied from 6 to 12 in either group (table 2). The frequency of other symptoms like disturbed consciousness, gaze deviation or hemianopia was rare (0–2 per 13 patients) and could not influence significantly the results of the final analysis, in spite of score values attributed to their assessment.

The neurological deficit in PGI₂ treated patients was lower than the control patients by 5.50 scores and this is attributed entirely to randomization. Therefore, only a difference in scores (T₀—Tₙ) could be used for analysis within the groups and between the groups. The ultimate result of the prostacyclin treatment was an improvement by 4.59 scores on average, and as seen in table 4, it would be reasonable to assume that this improvement was achieved during the first 6 hours of PGI₂ infusion and it was maintained thereafter. The disappearance of statistical significance of this beneficial effect 2 weeks later is mainly due to the spontaneous improvement which occurred in the placebo group. It is difficult from this pilot study to evaluate the clinical importance of the immediate beneficial effect of the PGI₂ treatment, although it has been statistically significant.

Only patients with completed strokes entered this study. Exclusions were made at the entrance to diminish risk of possible unfavourable effects of prostacyclin in diabetics, renal damage, severe cardiac arrhythmias, circulatory insufficiency and infections.

**Table 3** Analysis of Scores Inside Placebo (PL) and Prostacyclin (PGI₂) Groups

<table>
<thead>
<tr>
<th>Time</th>
<th>Scores Mean ± SD</th>
<th>Median</th>
<th>Difference in time</th>
<th>Difference in scores (D)</th>
<th>Student's t test</th>
<th>Wilcoxon's test</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀</td>
<td>21.3 ± 7.3</td>
<td>20</td>
<td>0.31</td>
<td>0.331</td>
<td>NS†</td>
<td>7.5</td>
</tr>
<tr>
<td>T₁</td>
<td>21.0 ± 8.4</td>
<td>19</td>
<td>0.54</td>
<td>0.712</td>
<td>NS</td>
<td>12.5</td>
</tr>
<tr>
<td>T₂</td>
<td>20.8 ± 7.4</td>
<td>19</td>
<td>2.38</td>
<td>1.581</td>
<td>NS</td>
<td>19.0</td>
</tr>
<tr>
<td>T₃</td>
<td>18.9 ± 10.1</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4** Final Analysis of Differences in Scores Between Placebo vs Prostacyclin Groups (df = 24)

<table>
<thead>
<tr>
<th>Difference in time</th>
<th>Difference in scores</th>
<th>Student's t test</th>
<th>Mann-Whitney's U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀—T₁ *</td>
<td>4.23</td>
<td>2.982 &lt;0.01</td>
<td>31.0 &lt;0.01</td>
</tr>
<tr>
<td>T₀—T₂</td>
<td>5.23</td>
<td>3.505 &lt;0.01</td>
<td>30.5 &lt;0.01</td>
</tr>
<tr>
<td>T₀—T₃</td>
<td>4.31</td>
<td>1.751 NS†</td>
<td>63.0 NS</td>
</tr>
</tbody>
</table>

* T₀ — before infusions.
  T₁ — 6 hrs after infusion started.
  T₂ — 54 hrs after commencement of the treatment.
  T₃ — 2 weeks after commencement of the treatment.
  †NS — non-significant.

**Figure 1.** Scores ascribed to individual patients at T₀ to T₃ in the placebo and PGI₂ groups.
The results of our pilot study indicates the need for further clinical trials of prostacyclin in the treatment of ischaemic stroke. Since the significant therapeutic effects of prostacyclin were seen as long as the treatment was continued, e.g. up to 54 hours, the most obvious approach would be to extend this treatment for a longer period of time, e.g. up to two weeks. Other options may include administration of prostacyclin in conjunction with heparin and indomethacin,13 with aspirin,4 or with a thromboxane synthetase inhibitor.20 One may also consider the possibility of changing dosage of prostacyclin, the replacement of intermittent regimen of infusion with a continuous one, using a stable long-acting analogue of prostacyclin or releasers of endogenous prostacyclin.22 Benefits were achieved in patients with retinal vein occlusion,7 and with acute myocardial infarction,23 who had been treated with prostacyclin. Patients with ischaemic stroke might benefit as well if prostacyclin infusions were given at the earliest possible stage of the disease. In conclusion, our present data suggest the need for further modified controlled studies of the treatment of cerebral ischaemia with prostacyclin alone or in combination with other drugs.

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References

14. Gryglewski RJ, Nowak S, Kostka-Trabka E, Kusmierczei J, Dem-
CAFFEINE is present in a wide variety of beverages, food substances and over-the-counter drugs. \(^1\)\(^2\) Large numbers of people of all age groups consume this substance in some form or other. Approximately twenty to thirty percent of the general population have been found to ingest more than 500-600 mg of the drug daily. \(^3\)\(^4\) Caffeine-containing beverages and foods are served in most hospitals, and patients with a wide variety of diseases consume it.

Cerebral vasoconstrictive effects of caffeine are well established. \(^5\)\(^6\) Several investigators have reported on the reduction in cerebral blood flow (CBF) induced by intravenous administration of the drug. These reports do not, however, address the more clinically relevant issue of the effects of small oral doses of the drug (comparable to the quantities in which it is usually consumed and the drug daily). \(^7\)\(^8\) Caffeine-containing beverages and foods are served in most hospitals, and patients with a wide variety of diseases consume it.

Cerebral vasoconstrictive effects of caffeine are well established. \(^5\)\(^6\) Several investigators have reported on the reduction in cerebral blood flow (CBF) induced by intravenous administration of the drug. These reports do not, however, address the more clinically relevant issue of the effects of small oral doses of the drug (comparable to the quantities in which it is usually consumed in daily life) on cerebral circulation. Similarly, no information is available on the duration of the change in cerebral circulation thus induced. In a recent study, we found significant reductions in CBF 30 minutes after oral administrations of 250 and 500 mg of caffeine. \(^9\) The two doses did not result in significantly different intensity of associated CBF reduction. The present project was designed to evaluate duration of caffeine induced cerebral vasocostriction and to extend the results of the above mentioned open trial by using a double-blind, placebo controlled design.

**Method**

Volunteer subjects were recruited through local advertising. They were carefully screened for physical and mental disorders. Those who gave a history of consuming more than three cups of coffee, tea or cola per day or any caffeine containing drug were excluded. Similarly, subjects with a history of alcohol and substance abuse were also excluded. Participants were required to remain medication free (prescription and over-the-counter) for a minimum of two weeks prior to the study. Subjects were instructed to abstain from all caffeine containing substances for at least two hours before the experiment.

First, a venous blood sample was obtained for the determination of hemoglobin values. This was required for the computation of the CBF values (see below). Regional cerebral blood flow was measured three times in each subject under identical laboratory conditions. Immediately after the first CBF measurement, subjects received either 250 mg of caffeine or a placebo with lemonade under double-blind conditions. The drug/placebo administrations were completed in less than 5 minutes. Subjects were assigned to the drug and placebo groups on a random basis. Blood flow...
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