Intravenous Prostacyclin in Acute Nonhemorrhagic Stroke: A Placebo-Controlled Double-Blind Trial


for The Prostacyclin Study Group

The therapeutic efficacy of prostacyclin in nonhemorrhagic cerebral infarction was assessed in a placebo-controlled double-blind trial. A total of 80 patients with stroke onset within 24 hours were randomized into placebo (37 patients) and prostacyclin (43 patients) groups. Demographic data and risk factors were comparable. Patients in the prostacyclin group received a continuous i.v. infusion of prostacyclin at an average rate of 8.5 ng/kg/min for an average of 64 hours. The placebo group received vehicle only in a similar fashion. During treatment hemodynamic changes were more prominent in the patients receiving prostacyclin and included reduction of systolic and diastolic blood pressure and increase in pulse rate. In contrast there was only a slight (but significant) reduction of diastolic blood pressure in the placebo group. Neurologic deficit scores were determined on admission, at Day 3, and at Weeks 1, 2, and 4. Mean neurologic deficit scores upon entry were comparable in the placebo and prostacyclin groups, and a significant improvement in the score for neurologic deficit was noted in both. The placebo group tended to fare better throughout the study, with a significant difference in neurologic deficit score favoring the placebo group at Week 2 (p = 0.0048). Two patients in the placebo and one in the prostacyclin group died. The only difference in adverse reactions was flushing (6 patients in prostacyclin vs. 0 in placebo group, p<0.05). The results of this study suggest a lack of therapeutic efficacy of prostacyclin in a defined population of patients with nonhemorrhagic cerebral infarction. Stroke 1987;18:352-358

The medical management of ischemic stroke has been directed mainly at the inhibition of thrombosis and coagulation.1 Among the therapeutic agents currently employed in the medical management of cerebral ischemia, only aspirin, an antiplatelet agent, has been proven in rigorous clinical trials (employing randomized, double-blind, placebo-controlled protocols) to show a moderate efficacy in reducing stroke and death in patients with transient ischemic attacks.2-4 Prostacyclin (PGI2, epoprostenol) is a potent platelet antiaggregant and vasodilator primarily synthesized by vascular endothelial cells from arachidonic acid (AA). AA released locally during cerebral ischemia is rapidly metabolized by cyclooxygenase to lipid peroxides and prostanoids, or by lipoxygenase to hydroxy fatty acids and leukotrienes.5-6 With the notable exception of PGI2, the formation of AA metabolites such as prostaglandin (PG) D2, PGE2, PGF2α, PGH2, thromboxane A2 (TXA2), and leukotrienes may interfere with brain perfusion.6-10 Of the vasoactive prostanoids, TXA2 and PGI2 are two of the most potent. They appear to affect hemostasis and vascular integrity in different pathologic processes by modifying the platelet-vessel wall interaction.8,11,12 TXA2 stimulates platelet aggregation and vasoconstriction. PGI2, on the other hand, inhibits platelet aggregation and causes vasodilation. Although the pathophysiology of cerebral ischemia has not been fully elucidated, one intriguing hypothesis is that TXA2-PIG1 imbalance8,13 may cause platelet activation14-15 and microcirculatory stasis leading to the "no reflow phenomenon."16-19

The claimed benefit of exogenous PGI2 in several peripheral thromboembolic disorders20-21 has encouraged its trial in ischemic stroke in both animals22-23 and humans.24-26 Results of the initial studies of the effectiveness of PGI2 in reducing ischemic brain damage have differed, but the results of all 3 human open-label trials of PGI2 in ischemic stroke appeared to be favorable.24-26 The present study was undertaken to assess the potential therapeutic effectiveness of PGI2 in acute nonhemorrhagic strokes employing a randomized, double-blind and placebo-controlled design.

Subjects and Methods

A total of 80 patients from 5 medical centers were enrolled into the protocol (see Appendix 1). The study
protocol was approved by the Institutional Review Board for Human Research at each center.

Eligibility

Adult patients (at least 21 years of age) of either sex with onset of symptoms within 24 hours were studied. All gave informed consent. Patients who had any of the following conditions were excluded: 1) severe impairment of sensorium (stupor or coma) or psychiatric disturbance; 2) participation in an experimental drug study within 9 half-lives of the experimental drug used; 3) indication by cranial computed tomography (CT) of intracranial pathology other than ischemic stroke; 4) active organ or systemic disorders including malignant hypertension (blood pressure persistently >200 mm Hg systolic or 120 diastolic), congestive heart failure, or myocardial infarction; 5) increased bleeding tendency including heparin administration within the preceding day.

Stratification and Randomization

The patients were stratified into thrombotic and embolic strokes based on clinical findings. Patients with an accepted cardioembolic source (such as atrial fibrillation, rheumatic or other valvular disease with or without prosthetic valve, and other supporting features including relatively young age and a lack of atherosclerotic risk factors) were considered to have embolic stroke. Patients without these features were considered to have thrombotic stroke. Patients in each group at each center were then randomized into PGI 2 and placebo groups in a double-blind fashion.

Procedures

Screening. A complete history and physical examination was conducted. Electrocardiogram (ECG), chest x-rays, cranial CT, and admission laboratory tests including complete blood count, erythrocyte sedimentation rate (ESR), prothrombin time (PT), partial thromboplastin time (PTT), bleeding time, serum electrolytes (sodium, potassium, chloride, and bicarbonate), serum chemistry (glucose, urea nitrogen, calcium, creatine, uric acid, total protein, albumin, cholesterol, triglyceride, bilirubin, alkaline phosphatase, and creatine phosphokinase) were obtained before initiation of therapy. The same laboratory tests were also obtained 6 hours after the initiation of treatment, at the end of treatment (Day 3), and upon discharge at the end of the first week.

Treatment. Patients received an i.v. infusion of either PGI 2 or placebo for 72 hours. PGI 2 sodium (epoprostenol sodium, Cycloprostin, synthesized by the Upjohn Co. and formulated by the Wellcome Found.) was supplied as a freeze-dried sterile powder. It was dissolved immediately before use in a diluent containing NaCl 0.147% w/v, glycine 0.188% w/v, and sodium hydroxide and diluted with normal saline to provide a solution of pH 10 for i.v. infusion. The infusion was started at 1 ng/kg/min, and the rate was increased every 30 minutes while blood pressure and heart rate were closely monitored until intolerance or a maximum rate of 10 ng/kg/min was reached. The infusion was continued for 72 hours, with a gradual reduction of the dose during the last 12 hours to avoid the possibility of rebound platelet hyperfunction, which has been reported after abrupt discontinuation. In the placebo group patients received diluent in normal saline in an identical fashion.

Adverse Reactions

All adverse reactions reported by patients or neurologists were recorded. When in the opinion of the investigator the potential risk from adverse reactions outweighed the therapeutic benefits, the infusion was reduced or discontinued.

Assessment of Therapeutic Effectiveness

A weighted scale was employed to grade neurologic deficits. The scale ranged from a normal total score of 100 (motor, 30; cranial nerves, 20; sensorium, 15; speech, 15; cerebellar, 10; reflexes, 5; sensory, 5) to lower scores for neurologic dysfunction (see Appendix 2). The grading system has been validated in previous studies. Grading of neurologic deficits was done by the same physician investigator at entry, at termination of therapy (Day 3), at Weeks 1 and 2, and the end of the study (Week 4). An overall assessment of the therapeutic efficacy as effective, indeterminate, or not effective was also made at the study terminus by the same investigator who was blind to the therapeutic code. A list of participating neurologists is included in Appendix 1. Coinvestigators who graded the neurologic deficits were attending neurologists, fellows in cerebrovascular disease, or chief residents in neurology.

Statistical Analysis

Data are expressed as mean ± SD where applicable. The neurologic scores and other quantitative variables such as vital signs were analyzed by one-way analysis of variance (ANOVA) to determine if there was a significant difference between the PGI 2 and placebo groups. The paired t test was used to assess the time-dependent changes including neurologic scores, blood pressure, and laboratory tests within PGI 2 and placebo groups. Qualitative factors such as overall assessment of therapeutic effectiveness, adverse reactions, and risk factors were analyzed by Fisher's exact test. A p value <0.05 was considered significant with a two-tailed test.

Results

Demographic Data

Table 1 summarizes the clinical stratification of the patients. Since the number of patients with embolic stroke was not sufficient for independent statistical analysis and the stratification into embolic and thrombotic strokes was based on the clinical picture and cannot be resolved with full certainty even after exhaustive diagnostic studies, the final analysis of therapeutic effectiveness combined thrombotic and embolic stroke. Demographic data is shown in Table
2. There was no significant difference between the 2 groups for sex, race, age, or weight. The risk factors for stroke are summarized in Table 3. There was no significant difference in the frequency of patients with risk factors except transient ischemic attacks, which were more frequent in the placebo group (12 vs. 6, \( p < 0.05 \)), and diabetes, which predominated in the PGI\(_2\) group (9 vs. 2, \( p < 0.05 \)). Abnormalities on chest x-ray, cranial CT, and ECG on entry were comparable in the 2 groups (Table 4).

**Infusion of Study Medication and Effects on Nonneurologic Parameters**

The average infusion rate for the PGI\(_2\) group was 8.5 ng/kg/min, and the mean infusion time was 64.0 hours. The placebo group received an average of 9.9 ng/kg/min equivalent of vehicle for an average of 60.6 hours. The infusion of PGI\(_2\) was initiated at an average interval of 15.3 hours after the onset of stroke compared with 17.4 hours for the placebo group. Table 5 summarizes the changes in blood pressure and pulse rate before and after infusion. Within the PGI\(_2\) group, there was a significant reduction of both systolic and diastolic blood pressure and a significant increase in pulse rate at the end of the PGI\(_2\) infusion. In the placebo group a slight reduction in diastolic pressure was noted at the end of vehicle infusion compared with that before infusion. Between groups, no difference in systolic or diastolic blood pressure was noted, but the pulse rate was slightly higher in the PGI\(_2\) than the placebo group at the end of infusion (PGI\(_2\), 78.8 \pm 11.5 vs. placebo, 74.6 \pm 12.6, \( p = 0.022 \)) (Table 5). The platelet count, PT, PTT, and bleeding time at 6 hours after the initiation of infusion, Day 3, and Week 1 did not vary from at entry. No difference in these parameters between groups was noted. Minor changes in laboratory values occurred with approximately equal frequency in the 2 patient groups. All these changes fell within the normal ranges and were not significantly different between the placebo and PGI\(_2\) groups except ESR, which was slightly elevated in the PGI\(_2\) group at the end of the first week (PGI\(_2\), 39.4 \pm 22.3; placebo, 33.4 \pm 21.5; \( p < 0.05 \)). Whether this is a spurious finding in repeated tests of significance remains to be determined.

**Neurologic Outcome**

In the overall assessment of therapeutic efficacy, treatment was considered effective in 8 patients (18.6%) in the PGI\(_2\) group and in 10 (27.0%) in the placebo group. Treatment was not effective in 19 patients (44.2%) in the PGI\(_2\) group compared with 12 (32.4%) on placebo. There were approximately equal numbers of patients assessed indeterminate in the PGI\(_2\) (16 patients, 37.2%) and placebo groups (15 patients, 40.5%). The delay from onset of stroke to PGI\(_2\) treatment was 20.2 \pm 4.4, 13.7 \pm 7.8, and 14.5 \pm 5.7 hours, respectively, for the effective, indeterminate, and not effective patients.

Figure 1 shows the average neurologic scores for the PGI\(_2\) and placebo groups on entry (screen), Day 3, and Weeks 1, 2, and 4. The baseline neurologic scores were comparable for PGI\(_2\) (64.2) and placebo (62.9). None of the study subjects had complete resolution of neurologic deficits on examination on Day 3. No difference in neurologic scores was noted between the PGI\(_2\) and placebo groups during the trial except at

### Table 1. Randomization and Stratification of Patients

<table>
<thead>
<tr>
<th>Types of stroke</th>
<th>PGI(_2)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic</td>
<td>38 (88%)</td>
<td>28 (76%)</td>
</tr>
<tr>
<td>Embolic</td>
<td>5 (12%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Total</td>
<td>43 (100%)</td>
<td>37 (100%)</td>
</tr>
</tbody>
</table>

### Table 2. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>PGI(_2)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (58%)</td>
<td>24 (65%)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (42%)</td>
<td>13 (35%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>20 (47%)</td>
<td>21 (57%)</td>
</tr>
<tr>
<td>White</td>
<td>22 (51%)</td>
<td>16 (43%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>63.2</td>
<td>65.1</td>
</tr>
<tr>
<td>SD</td>
<td>12.2</td>
<td>12.5</td>
</tr>
<tr>
<td>Range</td>
<td>33-88</td>
<td>40-84</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>160.4</td>
<td>171.7</td>
</tr>
<tr>
<td>SD</td>
<td>41.0</td>
<td>38.4</td>
</tr>
<tr>
<td>Range</td>
<td>105.8-256.6</td>
<td>102.5-264.6</td>
</tr>
</tbody>
</table>

### Table 3. Number of Patients With Risk Factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>PGI(_2)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attack*</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Smoking</td>
<td>24</td>
<td>23</td>
</tr>
</tbody>
</table>

*Significant difference in frequency (\( p < 0.05 \)) between the PGI\(_2\) and placebo groups.

### Table 4. Frequency of Abnormal Chest X-rays, CT Scan, and ECG

<table>
<thead>
<tr>
<th></th>
<th>PGI(_2)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Abnormal</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Chest x-rays</td>
<td>20 (51%)</td>
<td>19 (49%)</td>
</tr>
<tr>
<td>CT scan</td>
<td>15 (37%)</td>
<td>26 (63%)</td>
</tr>
<tr>
<td>ECG</td>
<td>12 (29%)</td>
<td>29 (71%)</td>
</tr>
</tbody>
</table>

% indicates percent of patients in the PGI\(_2\) or placebo group.
Week 2 when those receiving placebo had a significantly better score ($p = 0.0048$). Within both the placebo and PGI$_2$ groups a tendency for neurologic scores to improve with time was noted. Within the PGI$_2$ group, these scores were significantly better than baseline at Weeks 2 and 4. In the placebo group, improvement in neurologic scores was significant at Day 3, and Weeks 1, 2, and 4.

A separate analysis of each of the 7 function categories revealed significant improvement from baseline during the trial in 5 categories for the placebo and in 3 for the PGI$_2$ groups (Table 6).

**Medical Events**

One patient receiving PGI$_2$ and 2 on placebo died during the trial. The patient who received PGI$_2$ and died had a slight worsening of neurologic deficit on Day 2 and suffered a second, fatal stroke 6 days after completion of the PGI$_2$ infusion. One placebo patient became comatose and died on the second day of infusion. Another died of cardiac arrest during the second week. None of the deaths is believed to be related to the study medication. Other medical events noted during infusion are summarized in Table 7. There was no difference in the frequency of adverse reaction except for flushing, which was noted in 6 patients on PGI$_2$ and 0 on placebo.

**Discussion**

The results of this study failed to establish any therapeutic efficacy for PGI$_2$ in a defined population of patients suffering acute nonhemorrhagic strokes. A

**Figure 1.** Mean neurologic scores for the prostacyclin and placebo groups. The improvement in neurologic scores was significant on Day 3, Weeks 1, 2, and 4 in the placebo group (x); and only on Weeks 2 and 4 in the prostacyclin group (●). No difference in neurologic score was noted between groups except at Week 2 when placebo group was significantly better ($p = 0.0048$).
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Table 6. Significant Improvement in Neurologic Function by Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>PGI2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Improved (Week 4)</td>
<td>Improved (all periods)</td>
</tr>
<tr>
<td>Cranial nerves</td>
<td>Improved (all periods)</td>
<td>Improved (all periods)</td>
</tr>
<tr>
<td>Mentation</td>
<td>—</td>
<td>Improved (Week 2)</td>
</tr>
<tr>
<td>Speech</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Improved (Week 2)</td>
<td>—</td>
</tr>
<tr>
<td>Sensory</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Improved (Week 4)</td>
<td>Improved (Weeks 1 and 2)</td>
</tr>
</tbody>
</table>

similar conclusion has been reached in another double-blind trial using a lower dose and intermittent administration of PGI2. The improvement in neurologic score with PGI2 during our trial may confirm the impression of therapeutic benefit reached in open-label trials. Those receiving placebo, however, fared slightly better than those on PGI2, emphasizing the need for appropriately controlled studies in the assessment of prospective therapeutic agents.

The results of our trial and another clinical trial do not completely exclude a role for PGI2 efficacy in the treatment of acute cerebral ischemia. PGI2 may not have been administered early enough to prevent irreversible ischemic changes. Also, the doses used here and in the British study might not be sufficient to inhibit platelet aggregation or cause disaggregation despite the observation of reduced in vivo platelet activation in one open-label trial. The duration of the PGI2 infusion was selected somewhat arbitrarily and might not be optimal.

In this study the PGI2 infusion was titrated by patient tolerance or until a maximum infusion rate of 10 ng/kg/min was reached. The mean infusion rate achieved in the PGI2 group was 8.55 ng/kg/min, indicating that even if higher doses of PGI2 are efficacious in cerebral infarction the therapeutic index is likely to be low. PGI2 is a potent vasodilator, but given i.v. at a rate of 4–5 ng/kg/min, human volunteers had a slight decrease in cerebral blood flow. The hypotensive effect of PGI2 in the setting of impaired autoregulation could compromise cerebral flow in the ischemic region and offset any direct beneficial effect. In the overall assessment, those whose treatment was considered effective were infused at an average of 20.2 hours after stroke onset in comparison with 13.7 hours in the ineffective and 14.5 hours in the not effective group. This suggests that earlier initiation of treatment is not more efficacious. A lack of PGI2 effect might result from the actions of other products such as PGE1, PGE2, TXA2, leukotrienes, and free radicals, which are generated during the posts ischemic activation of AA metabolism. Their detrimental effects may not be offset by increased PGI2 levels in ischemic tissue. The finding, for instance, that PGI2 in combination with indomethacin and heparin, but not by itself, facilitates ischemic neuronal recovery and posts ischemic microcirculatory perfusion suggests that inhibition of the production of cyclooxygenase metabolites other than PGI2 may be necessary to constrain ischemic damage. Future therapeutic attempts to reduce brain damage following cerebral infarction probably should be aimed at the development of PGI2 analogs without hypotensive action and the concurrent use of other agents to block the generation of other arachidonate metabolites in the ischemic brain.

Appendix 1


Monitoring and Method Committee: O.I. Linet, D.C. Huang, and J.C. Kent.

Participating Centers: University of Texas Medical Center, Houston, Texas (F.M. Yatsu, J.C. Grotta, L.C. Pettigrew Jr., and J.D. Gray); Medical University of South Carolina, Charleston, South Carolina (E.L. Hogan, C.Y. Hsu, J.D. England, D.B. O'Neal, J.G. Zoltani, and Subramaniam Moothathu); University of Alabama, Birmingham, Alabama (R.E. Faught Jr. and Ben Lucy); Cleveland Clinic, Cleveland, Ohio (A.J. Furlan); University of Oregon Health Sciences Center, Portland, Oregon (B.M. Coull, V.T. Miller, A.B. Shaw, and R.W. Hart).


Appendix 2

Neurologic Grading System

(Total score in normal subjects is 100)

I. Mentation (30)
A. Sensorium and orientation (15)
Alert and oriented

Table 7. Medical Events During Infusion

<table>
<thead>
<tr>
<th>Event</th>
<th>PGI2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Flushing*</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Worsening of neurologic deficits</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Restlessness, agitation, confusion</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*Significant difference in frequency (p < 0.05) between PGI2 and placebo groups.
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Confused or disoriented .......................... 10
Lethargic ........................................... 5
Stupor or coma ..................................... 0

#### B. Speech and language (15)
- No disturbance .................................... 15
- Mild fluency, comprehension or naming disturbance not significantly affecting communication ..................... 12
- Moderate to severe nonfluency with good comprehension ........................................... 10
- Predominantly fluent speech with poor comprehension ........................................... 5
- Global aphasia ..................................... 0

#### II. Cranial nerves (20)
- Normal ........................................... 20
- Inattention hemianopsia .......................... 18
- Extraocular muscle palsies or paralysis ........... 15
- VIIth nerve palsy, central or peripheral .......... 12
- Hemianopsia ....................................... 9
- Dysarthria .......................................... 7
- Dysphagia .......................................... 3
- Respiratory deficits .................................. 2
- Akinetic mutism .................................... 1
- Apnea or stupor or coma ........................... 0

#### III. Cerebellum (10)
- Normal ........................................... 10
- Limb or trunk ataxia:
  - Mild ........................................... 5
  - Moderate ...................................... 2
  - Severe .......................................... 0
  - Untestable ....................................... 0

#### IV. Motor and gait (30)
- Normal ........................................... 30
- Monoparesis:
  - Arm (nondominant)
    - Mild ........................................... 25
    - Moderate ...................................... 20
  - Arm (dominant) or lower extremities
    - Mild ........................................... 22
    - Moderate ...................................... 17
- Hemiparesis:
  - Nondominant
    - Mild (able to walk) ............................ 16
    - Moderate (unable to walk) .................. 11
  - Dominant
    - Mild (able to walk) ............................ 15
    - Moderate (unable to walk) .................. 10

#### V. Reflexes (5)
- Normal ........................................... 5
- Asymmetrical deep tendon reflexes .............. 4
- Unilateral extensor plantar ....................... 2
- Bilateral extensor plantars ...................... 0

#### VI. Sensation (5)
- Normal ........................................... 5
- Unilateral primary sensory deficit
  - Mild ........................................... 3
  - Moderate ...................................... 2
  - Corticosensory deficit .......................... 1
  - Untestable or no response ...................... 0

### References


Key Words • cerebral infarction • clinical trial • human stroke • prostacyclin
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C Y Hsu, R E Faught, Jr, A J Furlan, B M Coull, D C Huang, E L Hogan, O I Linet and F M Yatsu

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