SUMMARY In the absence of universally accepted criteria for the medical treatment of stroke, we made a rigorously randomized comparative study of different treatments in 300 patients. One group of patients received only a general supportive treatment designed to ensure adequate supplies of water, electrolytes and calories, plus whatever was needed to prevent infection and correct extant associated pathology. Three other groups of patients were treated in the same way but were also given, respectively, one of the following medications: Hydergine (Sandoz) (a mixture of three ergot alkaloids), dexamethasone, and mannitol.

No statistically significant difference emerged among any of the treatment groups and the reference group in terms of objective therapeutic results. The authors concluded that, at least with the dosage used in this study, none of the treatments proved more useful than conventional supportive therapy in the first 10 days after a stroke.

TREATING PATIENTS with stroke is often unrewarding. As in other fields of medicine, the lack of a basic reference treatment for stroke has generated a multitude of drug therapies, each being thought of as a cure, only to be soon abandoned. It is likely that some deaths in the first several days after a stroke are due to cerebral edema around the infarcted area rather than to the infarct itself.1-3 Edema reaches its peak about 3 to 4 days after the stroke, and can be responsible for transtentorial herniation of the brain, rostrocaudal deterioration, and impaired cerebral blood flow. Drugs thought to reduce edema reduce intracranial pressure which can indirectly improve brain circulation. Those used in recent years include mannitol,4-7 corticosteroids,5, 8-11 and Hydergine,8, 12-15 each with conflicting reports of clinical effectiveness. We have studied these 3 therapies using 1) a large number of patients; 2) random selection for treatment; 3) each drug alone; 4) results from reliable clinical parameters; 5) data evaluated by a correctly designed statistical program.

Materials and Methods

We studied 300 patients with a diagnosis of stroke, hospitalized in the Emergency Medicine Division of the Polyclinic Hospital in Milan, during 1974 and 1975. The mean age for the whole group was 71 years. There were 110 men (mean age 69) and 190 women (mean age 73). Of these 241 were diagnosed as having an ischemic stroke, 189 in the carotid artery territory, 40 in the vertebrobasilar territory. In 12 the classification was uncertain. At hospitalization, each patient was assigned randomly to one of the following 4 treatment groups:

Group A. These patients received adequate water and electrolyte replenishment by intravenous infusion for the first 48–72 hours, and then a suitable caloric intake, in the form of a special standard diet if necessary, administered by stomach tube. These patients also received suitable antibiotics and additional treatments, such as digitalis, diuretics, tracheal aspiration and instillation of mucolytic agents, and bedsore prevention.

Group B. These patients received the same treatment as those in group A, plus a proprietary mixture of dihydroergocornine, dihydroergocristine and dihydroergocryptine, 0.3 mg each (Hydergine) in a daily dosage of 6 ampoules representing 1.8 mg of each alkaloid in the mixture.

Group C. Patients in group C received the same treatment as group A plus dexamethasone 24 mg daily, given in divided doses.

Group D. Patients received the same treatment as group A plus a solution of 20% hypertonic mannitol given i.v. 0.8–0.9 g/kg daily.

In all groups treatment was instituted between 3 and 24 hours after onset of symptoms. The period of observation was 10 days for all 4 groups.

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Patient Classification

In accordance with Locksley and Derouesné, we classified each patient as a case of hemorrhagic or ischemic stroke by the behavior of the following parameters. Cerebrovascular accidents were thought to be due to hemorrhage when the period of onset was less than 2 hours, impairment of consciousness progressing steadily to coma and a very recent history of headache and vomiting. Patients with cerebral hemorrhage generally had hypertension and bloody spinal fluid. Ischemic strokes had a longer period of onset, no history of headache or vomiting and clear spinal fluid. Overt hypertension indicated an ischemic or hemorrhagic stroke with indifferent probability, but a normal or low blood pressure was more suggestive of an ischemic than a hemorrhagic stroke.1, 33-38

We further divided patients with ischemic stroke into two groups; transient stroke (prompt resolution of the stroke diagnosis of cerebral embolism made on the strength of completed stroke (persistent stable neurologic impairment during the first few days after onset).37

Our clinical material also included 4 patients with a diagnosis of cerebral embolism made on the strength of young age, extant mitral valve disease, a history of previous embolization elsewhere in the body, and sudden onset.1, 36, 38

Patients were classified in terms of clinical evolution using a scoring system similar to that of Bauer and Tellez:8-21 (A) stroke in evolution in which both neurologic damage and impairment of consciousness changed during the observation period; and (B) established or stationary strokes, in which such changes did not occur.

Assessment of improvement or worsening was made by the following parameters: (1) state of consciousness at time of admission was classified at 4 levels, namely, wakefulness, somnolence, stupor, and coma;39 (all shifts from one level to another were recorded during the 10-day observation period); (2) neurologic signs of motor or sensory impairment with any change during the observation period, such as increasing or decreasing weakness or sensory impairment, were recorded.

Each patient was evaluated at 1, 2, 4, 7 and 10 days after hospitalization. Each evaluation required scoring the level of consciousness, language function, motor function and sensory function. Total numerical scores were obtained based on the presence or absence of 30 specific points. An increasing score was associated with worsening; a declining score with improvement.

The observation period was restricted to the first 10 days after the stroke. It was found that changes of focal motor and speech abnormalities were less reliable as a criterion for determining whether a stroke was improving or worsening during the first 10 days than was the state of consciousness.1

Results

On reviewing our results we excluded patients with transient cerebral ischemia because the prompt abatement of symptoms and signs (within 24 hours by definition) made it impossible to judge effectiveness of treatment. Patients with cerebral embolism were excluded because of the small number of cases. Patients with cerebral hemorrhage were excluded because an early mortality of 84%, regardless of the treatment, made analysis impossible.

Table 1 Two-by-Three Contingency Tabulation by Treatment Groups in Patients with Ischemic Cerebral Stroke (ICS)

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Ischemic cerebral stroke (ICS)</th>
<th>Evolutive</th>
<th>Established</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Improved</td>
<td>14</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Worsened</td>
<td>18</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>32</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Group B</td>
<td>Improved</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Worsened</td>
<td>18</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>33</td>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>Group C</td>
<td>Improved</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Worsened</td>
<td>19</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>34</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>Group D</td>
<td>Improved</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Unchanged</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Worsened</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>28</td>
<td>8</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worsened</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Group B</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Group C</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

The therapeutic results obtained in patients with ischemic stroke were used for statistical evaluation. The results are shown in tables 1 and 2. No significant differences were observed for any of the treatments given. Nor were there significant differences in outcome when strokes were divided into evolving and established stroke. Patients who were not in coma at the beginning of treatment did better than those with severely impaired consciousness. Older patients, in general, did worse than younger patients.

The three modes of treatment failed to show difference in outcome between treatment groups or between these and the reference group. A comparison with the reference group showed clearly that evaluation of an ischemic stroke was wholly independent of these treatments.

This finding could be interpreted to mean that treatment really has no effect in determining the course of a stroke, whether the wrong treatment was used or whether the wrong parameters of change were evaluated. To test the last hypothesis, we evaluated two possible sources of error: coma at the outset of stroke and age.

The role of coma as a major source of error was suggested by the very high mortality rate (86%) associated with coma.

Table 2 Statistical Comparison Between Control Group (A) and Three Treatment Groups (B, C, D) in Patients with Ischemic Cerebral Stroke (ICS)

<table>
<thead>
<tr>
<th>Interactions</th>
<th>Degrees of freedom</th>
<th>$X^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS (A) X ICS (B)</td>
<td>1</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>ICS (A) X ICS (C)</td>
<td>1</td>
<td>0.04</td>
<td>N.S.</td>
</tr>
<tr>
<td>ICS (A) X ICS (D)</td>
<td>1</td>
<td>0.028</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

$X^2$ = chi-square corrected for continuity; P = statistical significance; (other symbols same as in table 1).
in all 3 treatment groups as well as in the control group. Coma at onset of symptoms suggests so severe an anatomical injury as to make any drug treatment futile. When we recalculated the corrected chi-square values after eliminating patients with coma from the group, we found some evidence of effectiveness of dexamethasone and Hydergine treatment groups, but this did not reach statistical significance.

Age had no effect in determining outcome in the control group or in the groups treated with mannitol, Hydergine and dexamethasone. The mean age of patients who improved was less than 64.9 ± 2.08 and for those who became worse it was more than 64.9. Confining our statistical comparison to patients under this age limit and comparing them to their age mates in the control group, differences in outcome are below the minimum level of significance.

In conclusion, we were unable to demonstrate that any of the given treatments, in the dosages used in these trials, had a real influence on the clinical course of ischemic cerebral stroke, during the first 10 days after onset.

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