Therapy Against Brain Swelling in Stroke Patients

A RETROSPECTIVE CLINICAL STUDY ON 227 PATIENTS

BY LIVIA CANDELISE, M.D., ALVARO COLOMBO, M.D., AND HANS SPINNLER, M.D.

Abstract: The effectiveness of cerebral antiedema agents in stroke has been questioned. Animal and clinical work is inconclusive about steroids and osmotic drugs. A retrospective study of a continuous series of 227 stroke patients treated in the acute stage (some with dexamethasone alone, some with dexamethasone plus hyperosmotic mannitol infusions, and some without antiedema therapy) showed no significant difference in the ten-day survival rate. On this criterion, there is no ground for the systematic use of such agents against this type of brain swelling.

Additional Key Words: cerebrovascular disease, mannitol, dexamethasone

A retrospective study was undertaken to evaluate the short-term value of antiedema therapy in stroke patients. Brain swelling is one of the major consequences of a stroke, coming three or four days after the actual infarction. It may result in cingulate and central tentorial or uncal herniations, possibly leading during the acute stage to rostro-caudal deterioration of consciousness and ultimately to death. Moreover, edema around the ischemic area may worsen the neurological deficit. Drug therapy for stroke-induced brain swelling is based on the assumption that such edema is one of the crucial mechanisms of neurological worsening and death in the acute stage of a stroke.

Steroids and hyperosmotic infusions are used to control brain swelling of varying etiology and they are claimed to do this by different mechanisms: delayed intracellular fluid accumulation in the case of the former, and immediate extracellular fluid accumulation in the case of the latter. Experimental studies on steroids in ischemic brain damage are inconclusive: ineffective according to several studies, effective according to other studies. Many clinical reports are against the unselective use of steroids in acute stroke patients, although some suggest that the treatment is useful. With regard to osmotic drugs, urea was tried first, then mannitol, and finally glycerol. Concurrent treatment with dexamethasone and osmotic drugs has been proposed.

Methods

Patients

The 227 patients with cerebral infarction were admitted to the neurological wards of the Clinic for Nervous and Mental Diseases of the University of Milan (Italy) from 1965 to 1974. No a priori selection of the patients, other than that determined by the criteria below, has been made.

The 227 patients constitute a continuous series, encompassing three different therapeutic periods: vasodilator drug therapy, steroids, and steroids plus mannitol treatment. During all of these periods, comparable supportive, nursing, physiotherapeutic, dietary and general medical care was provided. None of the patients who entered the study received intensive care or neurosurgery.

Cerebrovascular disease samples are made up of heterogeneous subdivisions. The criteria used for inclusion in this study were: (1) clinical evidence of a completed stroke to one hemisphere, occurring up to 24 hours before admission, (2) treatment starting within 24 hours following the stroke, and (3) evidence (from history) that this was the first...
major cerebrovascular event for this patient. Some patients were excluded because (1) the etiology was an intracranial aneurysm or an arteriovenous malformation, (2) clouding of consciousness or death was not definitely related to cerebral disease, and (3) the treatment used could not be classified according to our criteria. Twenty-four percent of the original group of patients had to be excluded.

The patients treated with antiedema medication received drugs according to the following schedules:

1. Dexamethasone. Mean dosages were 8 mg t.i.d. (range, 4 to 16 mg). The drug was supplied in 250 ml of Ringer's solution or 5% glucose solution t.i.d. intravenously during the first seven days. In a small number of patients the same dosages of steroid were given intramuscularly.

2. Dexamethasone plus mannitol. The concurrent treatment always started from the beginning of the therapy. Infusions of 250 ml of 20% mannitol plus dexamethasone (as above) were administered t.i.d. for the first three or four days. On the following days, the patient received the same therapy as before.

STATISTICAL PROCEDURES

The principal items considered were: age, patients surviving at the tenth day following the stroke, presence or absence of a coma (provided the coma had been noted within the first 24 hours of the cerebral event), and the pharmacological treatment. Coma was defined as impaired consciousness at or below the diencephalic level.30

The patients were divided into three groups according to therapy: no antiedema therapy (64 patients), dexamethasone therapy (88 patients), and dexamethasone plus mannitol therapy (75 patients).

Four crossed criteria were used to classify the patients of each group: (1) survival rate at the tenth day following the stroke, (2) presence or absence of a coma, (3) age, as below or above 65 years, and (4) the three treatments listed previously.

The result was a four-dimension contingency table.31

Results

Of the 227 patients, 46% were women. The average age of all patients was 56.7 years. Twenty-six percent of the original patients had to be excluded because (1) the etiology was an intracranial aneurysm or an arteriovenous malformation, (2) clouding of consciousness or death was not definitely related to cerebral disease, and (3) the treatment used could not be classified according to our criteria. Twenty-four percent of the original group of patients had to be excluded.

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Discussion

The negative outcome of our comparisons, which precludes any hard inferences, may be due to the roughness of the ten-day survival as a criterion of effectiveness. And yet, our sample was large enough to elicit some evidence of a relationship between treatment and survival, if there was one. Cerebral edema following a stroke may not be as relevant to short-term survival expectancy as is generally thought; alternatively, it may not respond to the type of antiedema therapy we used. The first possibility is supported by Shaw's findings,1 which by no means bear out the predominance of stroke-induced brain swelling in the death mechanism, since for only a half of his patients death could be traced back to edema. Intracranial pressure studies in massive hemorrhage32 likewise fail to find it of key importance. Further, only 21% of Plum's33 106 hemispheric infarct patients showed a rapidly rostro-caudal deterioration of coma suggesting a clearcut supratentorial growing edema, while only 13% of Ng's35 353 stroke patients had severe brain swelling.

The second possibility corresponds with some clinical evidence which suggests that edema, mainly due to chronic focal lesions and certainly not prevailing in ischemic brain damage, responds to steroids.34 Otherwise, mannitol works only on the swelling that develops in a nonschemically damaged part of the brain.35

Even if nearly all cerebral lesions, both acute and

<p>| Distribution of 227 Stroke Patients According to a Four-Dimension Contingency Table |
|---------------------------------|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Therapies</th>
<th>Age</th>
<th>Survivors</th>
<th>Dead</th>
<th>Total</th>
<th>Survivors</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (64)</td>
<td></td>
<td>&lt;65</td>
<td>3</td>
<td>10</td>
<td>13</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥65</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>5</td>
<td>14</td>
<td>19</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Dexamethasone plus mannitol (75)</td>
<td></td>
<td>&lt;65</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥65</td>
<td>4</td>
<td>12</td>
<td>16</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>9</td>
<td>21</td>
<td>30</td>
<td>46</td>
<td>12</td>
</tr>
</tbody>
</table>

The frequencies within each cell of the four-dimension contingency table are given in Table 1. Table 2 shows the outcome of non-parametric analysis.

The principal items considered were: age, patients surviving at the tenth day following the stroke, presence or absence of a coma (provided the coma had been noted within the first 24 hours of the cerebral event), and the pharmacological treatment. Coma was defined as impaired consciousness at or below the diencephalic level.30

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The result was a four-dimension contingency table.31

Results

Of the 227 patients, 46% were women. The average age of all patients was 56.7 years. Twenty-six percent had diabetes and 9% had chronic atrial fibrillation with mitral valve disease. None of these concomitant variables had a significantly different distribution at the chi-square analysis.


candelise, colombo, spinller

<p>| TABLE 1 |
| Distribution of 227 Stroke Patients According to a Four-Dimension Contingency Table |
|---------------------------------|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Therapies</th>
<th>Age</th>
<th>Survivors</th>
<th>Dead</th>
<th>Total</th>
<th>Survivors</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (64)</td>
<td></td>
<td>&lt;65</td>
<td>3</td>
<td>10</td>
<td>13</td>
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<tr>
<td></td>
<td></td>
<td>≥65</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>5</td>
<td>14</td>
<td>19</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Dexamethasone plus mannitol (75)</td>
<td></td>
<td>&lt;65</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td>25</td>
<td>5</td>
</tr>
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<td></td>
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<td>≥65</td>
<td>4</td>
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<td>16</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>9</td>
<td>21</td>
<td>30</td>
<td>46</td>
<td>12</td>
</tr>
</tbody>
</table>
Continuous monitoring for midline shift and for inde- give antiedema therapy only to selected stroke tiedema treatment.

Tracranial hypertension and serial EMI scanning will and neurological deficits soon after stroke seem to be likely to develop. Rapid worsening of consciousness patients, i.e., those in whom acute cerebral edema is

Nevertheless, we think that brain swelling is not chronic, cause some degree of swelling, it is probably an oversimplification to classify them all by the type of the prevailing edema and the expected pharmacological responsiveness to the two main classes of antiedemic drugs.

Our feeling, supported only by scattered single observations, is that at least for some young patients (e.g., those with internal carotid occlusion or with massive embolic infarction) there is often clearcut response to mannitol plus dexamethasone treatment, both in terms of level of consciousness and survival. Nevertheless, we think that brain swelling is not systematically the leading factor in the acute prognosis of the stroke patient and therefore the antiedema therapy cannot dramatically change the mean life expectancy in a sample of unselected stroke patients.

Therefore, the wise course would seem to be to give antiedema therapy only to selected stroke patients, i.e., those in whom acute cerebral edema is likely to develop. Rapid worsening of consciousness and neurological deficits soon after stroke seem to be the most reliable clinical signs of developing edema. Continuous monitoring for midline shift and for intracranial hypertension and serial EMI scanning will possibly further help to single out the patients for antiedema treatment.

TABLE 2

<table>
<thead>
<tr>
<th>Interactions</th>
<th>D.F.</th>
<th>Chi-square</th>
<th>P</th>
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<tr>
<td>Therapy x survival x age</td>
<td>2</td>
<td>0.799</td>
<td>ns</td>
</tr>
<tr>
<td>x coma</td>
<td>2</td>
<td>3.605</td>
<td>ns</td>
</tr>
<tr>
<td>Therapy x survival x age</td>
<td>2</td>
<td>0.733</td>
<td>ns</td>
</tr>
<tr>
<td>Therapy x survival</td>
<td>2</td>
<td>1.419</td>
<td>ns</td>
</tr>
<tr>
<td>Survival x coma</td>
<td>1</td>
<td>3.633 &lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Survival x age</td>
<td>1</td>
<td>2.762</td>
<td>ns</td>
</tr>
</tbody>
</table>


CORRECTION


Measurement of Local Cerebral Blood Volume in Three Dimensions in Man — Kuhl DE, Reivich M, Nyary I, Alavi A (Cerebrovascular Research Center, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania 19104)

A method has been developed for the measurement of local cerebral blood volume in man with three-dimensional resolution. Transverse section imaging with an improved data processing technique enables a linear relationship to be obtained between the counts at any point in the scan and the radioactivity in the scanned object. This makes it possible to make absolute measurements of the concentration within the brain localized in three dimensions. In a series of five baboons the effect of blood pressure and arterial P_{CO_2} on local cerebral blood volume was examined. The following equation of the regression plane relating local cerebral blood volume (LCBV), P_{CO_2} and mean arterial blood pressure (MABP) was obtained:

\[ \text{LCBV} = 2.88 + 0.049 \text{P}_{CO_2} - 0.013 \text{MABP} \]

Local cerebral blood volume was measured in a series of eight patients and values ranged from 1.80 to 4.13 ml/100 gm depending on the location within the cross-section. The higher blood volumes coincided with cortical regions. In one patient abnormal vascularization in association with a tumor was clearly identified in the LCBV scan. In another, the reduction in LCBV caused by edema surrounding a small glioma was demonstrated in the LCBV scan which also showed improved regional circulation after steroid therapy.
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