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

Methods

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 patients constitute a continuous series, encompassing three different therapeutic periods (admittedly, with some overlapping at the interposed borderlines), namely that of a more or less defined vasodilator drug therapy, that of steroids, and that of 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...
Results
Of the 227 patients, 46% were women. The average age of all patients was 56.7 years. Twenty-six percent were above 65 years, and (4) the three treatments listed above 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 coma (provided the coma had been noted within the first 24 hours of the cerebral event), age, as below or above the diencephalic level.

The concurrent variables had a significantly different distribution at the chi-square analysis.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Age</th>
<th>Survivors</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (64)</td>
<td></td>
<td>3</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>25</strong></td>
<td><strong>16</strong></td>
<td><strong>41</strong></td>
</tr>
<tr>
<td>Dexamethasone (88)</td>
<td>&lt;65</td>
<td>5</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>10</strong></td>
<td><strong>23</strong></td>
<td><strong>33</strong></td>
</tr>
<tr>
<td>Dexamethasone plus mannitol (75)</td>
<td>&lt;65</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>8</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>13</strong></td>
<td><strong>20</strong></td>
<td><strong>33</strong></td>
</tr>
</tbody>
</table>

Table 1 shows the outcome of non-parametric statistical analysis. The only comparison of statistical significance was the interaction between presence and absence of coma and survival rate. This means that the patients who become comatose within the first 24 hours of onset have a significantly poorer life expectancy (67% dead) than noncomatose patients (24% dead).

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, 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 hemorrhage likewise fail to find it of key importance. Further, only 21% of Plum's 106 hemispheric infarct patients showed a rapidly rostro-caudal deterioration of coma suggesting a clearcut supratentorial growing edema, while only 13% of Ng's 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.

Otherwise, mannitol works only on the swelling that develops in a nonischemically damaged part of the brain.

Even if nearly all cerebral lesions, both acute and...
Continuous monitoring for midline shift and for in-give antiedema therapy only to selected stroke patients will help to single out the patients for antiedema 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.

### References


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 Pco2 on local cerebral blood volume was examined. The following equation of the regression plane relating local cerebral blood volume (LCBV), Paco2 and mean arterial blood pressure (MABP) was obtained:

\[ \text{LCBV} = 2.88 + 0.049 \text{Paco}_2 - 0.013 \text{MABP} \]

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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