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.

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 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
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 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,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’s106 hemispheric infarct patients showed a rapidly rostro-caudal deterioration of coma suggesting a clearcut supratentorial growing edema, while only 13% of Ng’s353 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.24 Otherwise, mannitol works only on the swelling that develops in a nonischemically damaged part of the brain.25

Even if nearly all cerebral lesions, both acute and chronic, could have some edematous component, it is possible that the antiedema therapy prevented death in only a minority of cases. The problem of whether the antiedema therapy had a beneficial effect in a large enough percentage of the patients, as in our sample with 30% survivors, awaits further studies.

**TABLE 1**

Distribution of 227 Stroke Patients According to a Four-Dimension Contingency Table

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Age</th>
<th>With coma (88)</th>
<th>Without coma (145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Survivors</td>
<td>Dead</td>
</tr>
<tr>
<td>None (64)</td>
<td></td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Dexamethasone (88)</td>
<td></td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Dexamethasone plus mannitol (75)</td>
<td>&lt;65</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>13</td>
<td>20</td>
</tr>
</tbody>
</table>
疗法对抗脑肿胀在中风患者

| 表 2 | 四维度方差分析频率 | 给定表 1
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>及时性</td>
<td>D.F.</td>
<td>Chi-square</td>
</tr>
<tr>
<td>疗法 × 年龄 × 年龄</td>
<td>2</td>
<td>0.799</td>
</tr>
<tr>
<td>疗法 × 年龄</td>
<td>2</td>
<td>3.605</td>
</tr>
<tr>
<td>疗法 × 年龄 × 年龄</td>
<td>2</td>
<td>0.733</td>
</tr>
<tr>
<td>疗法 × 年龄</td>
<td>1</td>
<td>3.633</td>
</tr>
<tr>
<td>年龄</td>
<td>1</td>
<td>2.762</td>
</tr>
</tbody>
</table>

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 pharma-

cological responsiveness to the two main classes of
anti-edema 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 an-
ti-edema 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 anti-edema 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 an-
ti-edema treatment.

References

1. Shaw CM, Alvord EC, Berry RG: Swelling of the brain follow-
ing ischemic infarction with arterial occlusion. Arch Neurol
1:161-177, 1959
2. Ng UKY, Nimmanitvaya J: Massive cerebral infarction with
severe brain swelling: A clinicopathological study. Stroke
1:158-163 (May-June) 1970
3. Weinstein JD, Toy FJ, Jaffe ME, et al. The effect of dex-
4. Reulen HJ, Hadjidi smartphones, Schürmann K The effect of dex-
amethasone on water and electrolyte content and on rCBF in
peripheral focal brain edema in man. In Reulen HJ, Schürmann K (eds):
Steroids and Brain Edema. Berlin, Springer-Verlag, p
239-252, 1972
5. Plum F, Alvord EC Jr, Posner JB: Effect of steroids on ex-
perimental cerebral infarction. Arch Neurol 9:571-573,
1963
vasculature obstruction produced by ischemia. J Neurosurg
30:50-54, 1969
7. Kahn K, Pranzarone GF, Newman T: Dexamethasone treat-
ment of experimental cerebral infarction. (abstract)
8. Siegel BA, Studer RB, Potchen EJ: Effect of dexamethasone
on triethyl tin induced brain edema and the early edema in
cerebral ischemia. In Reulen HJ, Schürmann K (eds): Ste-
roids and Brain Edema. Berlin, Springer-Verlag, p
113-121, 1972
9. Donley RF, Sundt TM: The effect of dexamethasone on the
edema of focal cerebral ischemia. Stroke 4:148-155 (Mar-
Apr) 1973
treatment methods of cerebral infarction edema. Stroke
4:1461-1464 (May-June) 1973
treatment methods of experimental cerebral infarc-
on the early edema following occlusion of the middle
cerebral artery in cats. In Reulen HJ, Schürmann K (eds):
Steroids and Brain Edema. Berlin, Springer-Verlag, p
127-137, 1972
13. Harrison MJG, Russell RWR: Effect of dexamethasone on ex-
perimental cerebral infarction in the gerbil. J Neurol
Neurosurg Psychiat 35:520-521, 1972
14. Dyken M, White PT: Evaluation of cortisone in the treatment
of cerebral infarction. JAMA 116:2-131-134, 1956
15. Hetzel BS, Lander H, Robson HN: Immediate treatment of
apoplexy. (correspondence) Brit Med J 1:1112, 1957
17. Tellez H, Bauer RB: Dexamethasone as treatment in
cerebrovascular disease. A controlled study in intracerebral
hemorrhage. Stroke 4:541-546 (July-Aug) 1973
18. Bauer RB, Tellez H: Dexamethasone as treatment in
cerebrovascular disease. A controlled study in acute cerebral
infarction. Stroke 4:547-555 (July-Aug) 1973
19. Russe H, Russe AS, Zohman BL: Cortisone in immediate
therapy of apoplectic stroke. JAMA 159:102-105, 1955
20. Roberts HJ: Supportive adrenocortical steroid therapy in
acute and subacute cerebrovascular accidents, with par-
ticular reference to brain stem involvement. J Amer Geriat
21. Rubenstein JK: The influence of adrenocortical steroids on
severe cerebrovascular accidents. J Nerv Ment Dis 141:291-
299, 1965
the effects of dexamethasone on acute stroke. Neurology
23. Javid M, Urea — new use of an old agent. Reduction of in-
tracranial and intraocular pressure. Surg Clin N Amer, p
907-928 (Aug) 1958
24. Wise BL, Chater N: The value of hypertonic mannitol solution
in decreasing brain mass and lowering cerebrospinal fluid
25. Shenkin HA, Goluboff B, Haft H: The use of mannitol for the
reduction of intracranial pressure in intracranial surgery. J
clinique et manometrique des solution hypertoneques et des
corticoïdes dans le traitement de l'hypertension in-

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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:

\[ LCBV = 2.88 + 0.049 \text{Paco2} - 0.013 \text{MABP} \]

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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