Dexamethasone as Treatment in Cerebrovascular Disease. 2. A Controlled Study in Acute Cerebral Infarction

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Abstract:
Dexamethasone as Treatment in Cerebrovascular Disease. 2. A Controlled Study in Acute Cerebral Infarction

Fifty-four patients with acute cerebral infarction were included in a double-blind study to evaluate Decadron® as therapy. When comparison of patients with similar levels of consciousness was made, there was no significant difference between those patients receiving Decadron® and those receiving placebo therapy.

Three patients developed gastrointestinal tract bleeding in the placebo group, but none in the Decadron®-treated group.

There was no good correlation between the clinical state of the patient and the CSF pressure, either on admission or during the 14-day course of the study.

Additional Key Words: Gl bleeding with use of steroids, CSF pressures in cerebral infarction, effect of steroids on CSF pressure

A prospective double-blind study was performed to evaluate the effectiveness of dexamethasone (Decadron®) as a treatment for acute cerebral infarction. The rationale for the use of steroid preparations has been to lessen the damaging effect of cerebral edema, increased intracranial pressure and a disturbed blood-brain barrier, as well as to counteract the "stress" factor associated with acute cerebral infarction. An earlier study had been done using dexamethasone in patients with intracerebral hemorrhage. There was no obvious significant advantage found with the use of dexamethasone in these patients.

Reports in the literature have discussed the usefulness of steroid therapy in the treatment of acute and subacute "strokes." In 1955, Sheely et al. reported on the beneficial effect of cortisone and hydrocortisone in two patients with acute cerebral infarction and in four patients with residual spastic hemiparesis. Russek et al. reported "dramatic clinical improvement" in 21 patients with acute stroke due to cerebral thrombosis or embolism who were treated with cortisone therapy. Roberts, in 1958, reported good results with the use of intramuscular cortisone acetate in nine patients who were critically ill. Most of his patients had brain stem involvement. No control patients were used in the preceding reports.

Dyken and White reported on the use of cortisone in the treatment of 36 patients with cerebral infarction. The treated patients received 300 mg cortisone daily for two days followed by gradual reduction to 50 mg daily within 21 days, at which time the drug was withdrawn. Cortisone was assigned as treatment on an alternate basis after the patients were classified according to severity, age, blood pressure and other data. There were 17 patients who received cortisone and 19 controls who received a placebo. There were 13 deaths in the cortisone group and 10 deaths in the placebo group. This difference, although not statistically significant, discouraged them toward further use of cortisone for cerebral infarction.

Hetzel et al. reported a double-blind treatment program in only 12 cases. Six received prednisolone tablets "in the dosage recommended" (quotation marks added), while six other patients received placebo. In each group three patients died, two improved and one did not improve. They discontinued the therapy at that point with the conclusion that use of large doses of cortisone was of no value.

Rubenstein reported on the use of dexamethasone in severe cerebrovascular accidents. Treatment consisted of either a placebo or 1 cc (4 mg) dexamethasone intravenously and 1 cc intramuscularly at the beginning of the study, followed by 1 cc...
intramuscularly every six hours for 72 hours. The house staff and attending staff were unaware of the nature of the drug given to the patients, or whether the patient was on drug or placebo. Of 19 patients with nonhemorrhagic cerebral infarcts, 13 had received dexamethasone and six had received a placebo. There were four deaths in the 13 patients treated with dexamethasone and four deaths in the six patients who received a placebo. Three of the four treated patients who died were begun on steroids late in the course of their disease, i.e., after brain stem injury had occurred, whereas none of the nine survivors had evidence of brain stem injury prior to treatment. Rubenstein was impressed by a definite improvement in level of consciousness, usually within 12 to 24 hours after dexamethasone was started, and suggested that the beneficial effects of dexamethasone may be due to the prevention of herniation of brain tissue and subsequent brain stem injury. He concluded that immediate mortality is reduced and level of consciousness may be improved when large doses of dexamethasone are instituted early in the course of a massive cerebral infarction.

In view of the evidence cited above, it was thought that a further controlled study of steroids in cerebral infarction would be indicated. While this study was in progress, Patten et al.9 reported on a double-blind study of the effects of dexamethasone on acute stroke. They concluded that dexamethasone can be a useful adjunct, especially in the more severe cases.

Methods

Only patients with disturbance in their level of consciousness were admitted to the study. Randomization was performed on a consecutive admission basis rather than according to the patient’s clinical status on admission. In retrospect, this has led to some problems with evaluating the data. Treatment was carried on for ten days with the final neurological assessment being made at the end of 14 days.

Criteria to be met for inclusion into this study were as follows: (1) Clinical evidence of acute cerebral infarction due to either occlusive cerebrovascular disease or cerebral embolism, (2) Impairment of the level of consciousness, (3) Clear cerebrospinal fluid or less than 300 red blood cells per cubic millimeter, (4) Absence of history of gastrointestinal bleeding or symptomatic duodenal ulcer, (5) Diagnosis made and treatment started within the first 48 hours following the onset of cerebral infarction.

Upon inclusion in the study, each patient had a complete neurological examination which was recorded on a specially prepared evaluation sheet. An arbitrary point value was assigned to various functions so that a scoring system was available for patient comparison, with the maximum normal score being 68 points. The variables measured were: level of consciousness (7 points); mental function, including orientation, attention, digit span, simple arithmetic, etc. (38 points); cranial nerve function (5 points); motor system function (11 points); reflex functions (3 points); and speech ability (4 points).

The levels of consciousness were defined as follows: deep coma (absent DTRs and pupillary reactions, corneal reflexes with no response to pain); coma (DTRs, pupillary reactions and corneal reflexes present but no response to pain); semicomma (nonspecific response to pain); deep stupor (purposeful response to pain); stupor (appropriate response to verbal stimuli); semi-stupor (lethargic, response slowed).

The arbitrary point value assigned to the neurological evaluation was as follows:

A. Level of consciousness

<table>
<thead>
<tr>
<th>Points</th>
<th>Clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Deep coma</td>
</tr>
<tr>
<td>2</td>
<td>Coma</td>
</tr>
<tr>
<td>3</td>
<td>Semicoma</td>
</tr>
<tr>
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<td>Deep stupor</td>
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<td>5</td>
<td>Stupor</td>
</tr>
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<td>6</td>
<td>Semi-stupor</td>
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B. Cranial nerves

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<tr>
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<td>4</td>
<td>Mild impairment</td>
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<td>Normal</td>
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<td>Decorticate rigidity</td>
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<td>3</td>
<td>Akinetic mutism</td>
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<td>Quadriplegia</td>
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<td>7</td>
<td>Hemiparesis</td>
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<td>Monoparesis</td>
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<td>9</td>
<td>Monoplegia</td>
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<td>10</td>
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<td>11</td>
<td>Normal</td>
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D. Reflexes

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<tr>
<td>2</td>
<td>Asymmetrical</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
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E. Speech

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<tr>
<td>3</td>
<td>Minimal dysphasia</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
</tr>
</tbody>
</table>

F. Mentation

A standardized testing method was used for each patient with the following point value: orientation and attention (15 points), digit span (10 points), mental arithmetic (9 points), and similarities and differences (4 points) (total, 38 points).

The maximum total of 38 points for mentation broken down into four categories was attained by the following:

A. Patients were tested for orientation and attention (15 points) by the following tests, with one point being given for each “correct” result: responds to pain; orients, turns toward or reaches for verbal or visual stimuli; can make basic needs known; can feed
A summary of data for the 54 patients analyzed in this study is found in table 1, arranged according to level of consciousness on admission.

Three patients in the placebo group and two patients in the treated group were excluded from the study prior to analysis. In the placebo group, one patient was receiving steroids for lymphocytic leukemia, and the etiology of her cerebral disease was in question. A second patient received some medication from another patient in the study who had just previously died in the hospital.

The study was conducted in two parts. Part 1 had 20 Decadron patients and 17 placebo patients. Part 2 contained eight Decadron patients and nine placebo patients. The second study was conducted because the Decadron and placebo groups in Part 1 were dissimilar in terms of initial severity. Unfortunately, this difference was not eliminated by the addition of the 17 patients in Part 2. Even though not statistically significant (p > 0.05), the placebo patients were clinically worse on admission than the Decadron patients in all categories. The two parts of the study are combined for analysis.

**Case Material**

A total of 54 patients admitted to the Neurology Services at Detroit General Hospital and Harper Hospital were included in this double-blind study. The average age was 66.2 years for those in the placebo group and 66.4 years for those in the Decadron group. There were 30 females and 24 males. Fifteen of the females were in the placebo group and 15 in the Decadron group. Of 24 males, 11 were in the placebo group and 13 in the Decadron group.

Of the 26 placebo patients, 14 had right cerebral infarction, eight had left cerebral infarction, and four had brain stem infarction. Of the 28 patients treated with Decadron, 14 had right cerebral infarction, 14 had left cerebral infarction, and no patients had brain stem infarction. Autopsies were performed on six patients in the placebo group and on four patients in the Decadron group. There was one discrepancy noted between the clinically diagnosed location of the infarction as compared to the autopsy finding; one patient with a right hemiplegia was diagnosed clinically as a left cerebral infarction. At autopsy a left medullary infarction was found.

Of the 26 placebo patients, eight had no RBCs in the CSF, 14 had 50 or less RBCs, and four had more than 100 RBCs. Of the 28 Decadron patients, 11 had no RBCs in the CSF, 10 had 50 or less, and seven had more than 100 RBCs. Of the total of 11 patients who had more than 100 RBCs in their CSF, all but one survived. The patient who died had 58 RBCs in her CSF. At autopsy an ischemic infarction of the medial and anterior portion of the left medulla was found. It would appear that the presence of RBCs or the number of RBCs in the CSF is not of specific prognostic value; nor does the presence of a few RBCs necessarily mean there has been a hemorrhagic infarction rather than an ischemic infarction.

**Material**

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### TABLE 1

Summary of Data for Total Series (No. = 54)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Admission consciousness level</th>
<th>Level at 14 days</th>
<th>Total initial score</th>
<th>Total score at 14 days</th>
<th>Most. score at adm.</th>
<th>Most. score at 14 days</th>
<th>Location of infarction</th>
<th>Result</th>
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<td>Semicoma</td>
<td>Died</td>
<td>12</td>
<td>0</td>
<td>1</td>
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<td>Brain stem</td>
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<td>0</td>
<td>Brain stem</td>
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<td>L cerebral</td>
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<td>2</td>
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<td>L cerebral</td>
<td>Died</td>
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<tr>
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Decadron Group (No. = 28)

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<th>Level at 14 days</th>
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<td>17</td>
<td>2</td>
<td>R cerebral</td>
<td>Worse</td>
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Dexamethasone in CVD. 2.

died. A third patient was found to have a brain tumor at the conclusion of the post-treatment investigation.

One patient in the Decadron group was excluded because she was given known steroids as treatment for septic shock before the study period had ended. A second patient in the Decadron group signed herself out of the hospital against medical advice on the second day of the study and therefore was excluded from analysis.

The level of consciousness at admission to study and number of mortalities are shown in table 2. There was an overall mortality rate at 14 days of 34.5% in the placebo group as compared to 17.3% in those treated with Decadron. However, in the placebo group there were six patients who were semicomatose on admission to the study as compared to only two in the “treat” group. Since all six of the semicomatose patients subsequently died, this has a great effect on the mortality rate in the placebo group.

The average admission score for the placebo group was 21.54 points as compared to an average admission score of 25.41 points for the “treat” group. This difference is statistically significant and precludes comparing the two groups as a whole unit. When all semicomatose patients were excluded from each group, the average admission score was 22.1 points for the placebo group and 26.2 points for the treated group. Although closer for comparison, the “treat” group was still a healthier group.

Of the maximum score of 68 points for the normal patient, 38 points were credited to the one variable of mental function. This may be considered an “overweighting” in one area. However, the actual average number of points accumulated in this category of mental function was only 5.23 in the placebo group and 6.86 in the treated group. This is some indication of the severity of illness of all patients admitted to the study and not unexpected in view of the admission criteria being a disturbance in the patients’ level of consciousness. By excluding the category of mental function, the average admission score for the placebo group was 16.31 points and for the treated group it was 18.21 points. This again demonstrates a failure of randomization and a problem in comparing the two groups.

Another uneven result of the randomized double-blind technique occurred in those 19 patients who were only semi-stuporous, for only seven were in the control group whereas 12 were in the “treat” group. Therefore, in general, the “placebo” and “treat” groups were not comparable regarding level of consciousness and overall condition, for the “treat” group had four fewer patients who were semicomatose (most severe disturbance of consciousness) and had five more patients who were only semi-stuporous (least severe disturbance of consciousness).

Results

A complete statistical evaluation of the test results was performed. The data were analyzed by Contingency Table Methods. The variables measured were: number of patients who died, level of consciousness, orientation and attention, cranial nerve functions, motor system functions, reflex functions, speech ability, and level of reaction to pain. These variables were measured at the time of admission to the study (Day 1) and again on Days 2, 4, 6, 8, 10 and 14. They were analyzed by an X² test for a three-way contingency table. This analysis was performed on the improvement from Day 1 for each patient. The analysis of the variables of cranial nerve function, orientation and attention was based on the number of patients alive on the given day. The other variables are based on the total sample. No statistically significant difference was found for any of the variables between the treatments.

On Day 2, four of the placebo group died. This is felt to be due to the fact that they entered the treatment in a more severe state (semicomatose) rather than to the lack of dexamethasone. There was no statistically significant difference in the death rates between the two groups. These deaths in the placebo group play an important role in the interpretation of the study. Excluding these early deaths, the two groups are similar for the other variables throughout the study. Including these deaths, the placebo group is always in a clinically worse condition than the treated group, but still not statistically significantly different.

In an effort to eliminate the inequality in degree of initial severity of the placebo and Decadron groups, a reanalysis was made by excluding the six semicomatose patients in the placebo group and the two semicomatose patients in the Decadron group. Even though the exclusion of these patients tended to provide a better comparability between the two groups, few statistically significant treatment differences were found for any of the measured variables. The results were similar to the original analysis which included all patients. The data were analyzed by the appropriate Chi-square procedure where possible. Two-way comparisons were made using Fisher’s Exact Test.

*Mr. G. M. Cohen, Merck, Sharp & Dohme Co.
The following variables were analyzed: (1) level of consciousness, (2) orientation and attention, (3) cranial nerve functions, (4) normal cranial nerves, (5) level of motor system function, (6) level of reflex response, (7) level of reaction to pain, and (8) level of speech.

For the statistical analysis, the variables were examined in two ways. Variables 1, 2, 3 and 4 (above) were considered first by the number (percent) of correct or positive responses for each of the categories within a variable. The percent response was then compared for placebo and Decadron. These variables also were examined by considering the change from the Day 1 level to Day X level (X = 2, 4, 6, 10 and 14-day examinations). The number (percent) of patients who changed during treatment was compared for placebo and Decadron, i.e., those who changed from a “yes” on Day 1 to a “no” on Day X, or vice-versa.

Variables 5, 6, 7 and 8 also were analyzed in two ways. First, the number (percent) of patients in each category was compared between the two treatment groups. Then the change from the Day 1 to the Day X level was examined. For these variables, however, the analysis was based upon those patients who either changed to a lower level (worsened), stayed at the same level (same), or changed to a higher level (improved).

In general, few statistically significant treatment differences were found for any of the parameters measured. In most cases, the effect appeared to be in favor of placebo. The specific results with some statistical significance are as follows:

(1) Under mentation and attention, on Days 4, 6 and 8, the response to “knows date” was significant at the 0.05 level in favor of placebo.

(2) Under cranial nerves, on Days 2, 4 and 6 the percentage of patients with “abnormal retina” was significant at the 0.05 level in favor of the Decadron group. It is difficult to relate this to the effect of Decadron, for this included all possible retinal abnormalities but excluded papilledema. In all the numbers of observation for the finding of papilledema, it was reported only once, that on Day 4 of a patient in the placebo group.

(3) In the level of reflex response, on Day 6 the percent of patients with improved response was significant at the 0.05 level in favor of the placebo group.

When excluding all patients who were semicomatose on admission, there are then 20 patients in the placebo group, of whom three (15%) died, as compared to 26 patients in the “treat” group, of whom four (15.4%) died (table 3). In the placebo group 15 patients (75%) were improved or unchanged as compared to 19 patients (73.1%) in the “treat” group. There were five patients (25%) in the placebo group who became worse or died, as compared to seven patients (26.9%) in the “treat” group. It is noted that the average point improvement per patient is the same for the placebo and Decadron groups (7.2 points). The average point worsening per patient is 5.0 points in the placebo group as compared to 10.7 points in the Decadron group. The average admission point score for the three patients in the placebo group who died was 21.3 points as compared to 25.0 points average for the four patients in the Decadron-treated group.

The data in the above paragraph are based on any degree of improvement, even if it were only one point. Arbitrarily selecting a 20% improvement from the admission score to the 14-day score as a basis for comparison, six of the 20 patients in the placebo group (30%) and 10 of 26 patients in the “treat” group (38.5%) achieved this 20% improvement. The six patients in the placebo group improved an average of 11.6 points per patient and the 10 patients in the “treat” group improved an average of 9.7 points per patient.

Table 4 is a day-by-day compilation of five variables in order to compare the clinical course of the patients in each group. The placebo group starts out with a slightly lower score in each category, but at the end of 14 days there is really very little difference.

Comparison was then made of the patients who were either in deep stupor or stupor at admission to the study. With this categorization there were 13 patients in the placebo group and 14 patients in the “treat” group (table 5). In the placebo group six
patients improved, four patients were unchanged, one became worse, and two patients died. In the "treat" group 11 patients improved, one patient was unchanged, none became worse and two patients died. Thus, there is very little difference between those patients who received placebo as compared to those who received Decadron.

Cerebrospinal Fluid Pressure
CSF pressures were obtained to determine if there was any correlation between pressure and the clinical state on admission, the subsequent clinical course, and whether on placebo or dexamethasone, and also to determine if the use of dexamethasone affected the CSF pressure. Reference to this has been made elsewhere prior to all the patients having been added to this study.10

Table 6 pertains to CSF pressures and level of consciousness. Three of the six semicomatose patients in the placebo group had elevated pressures, whereas none of the two semicomatose patients in the dexamethasone-treated group had elevated pressures. This finding is reversed in the patients in deep stupor. In all, 10 of the 26 patients (38.5%) in the placebo group had increased pressures as compared to 8 of 28 (28.5%) in the treated group.

Table 7 lists the possible correlations in somewhat more detail. Twelve (28.5%) of 42 subsequent readings were elevated in the placebo group as compared to 10 (19%) of 52 subsequent readings in the treated group. Four of ten patients with elevated CSF pressure in the placebo group died within 14 days, whereas only one of eight with elevated pressure died in the treated group. However, three of the four patients in the placebo group who died were semicomatose on admission, and none of the treated group with elevated CSF pressure were semicomatose. There does not seem to be a good correlation between the clinical state of the patient and the CSF pressure, or of the use of dexamethasone and the subsequent CSF pressures.

Complications
There were three patients who developed gastrointestinal tract bleeding in the placebo group and none in the "treat" group. This would at least demonstrate that the use of steroids in these acutely ill patients did not cause gastrointestinal bleeding. Conversely, it may have protected the patient from gastrointestinal bleeding by combating the "stress" of the intracerebral insult. There were no deaths in the three patients who developed gastrointestinal bleeding, although "treatment," which subsequently was found to be placebo, was terminated at the onset of the gastrointestinal bleeding.

Delayed Usage of Dexamethasone
The optimum time to use steroids in stroke, if not to be used in every case, would be in those patients

---

### Table 4

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*Figures in parentheses refer to number of patients.
admitted with normal consciousness but who then sometime after admission have a worsening in their level of consciousness. Therefore, a prospective study also was designed to include those patients. Treatment was carried out in a similar randomized double-blind manner as described previously in this report. However, only six patients were able to be included in this study, three in the placebo group and three in the Decadron "treat" group. There were two survivors and one death in the placebo group and one survivor and two deaths in the Decadron group. There was only one elevated CSF pressure (190 mm water) in these six patients. The number of patients is too small for further enumeration or statistical analysis.

Discussion

The results of this study are in contradiction to that of Patten et al. In their series of 31 patients, the 14 patients receiving Decadron had a 12% average improvement per patient, whereas the 17 patients receiving placebo had a 12% average worsening per patient. There were no deaths. The difference between the two groups was more significant in their severely ill patients, where the seven patients receiving Decadron showed a 23% improvement, and the eight patients receiving placebo had a 14% worsening.

In our series, excluding all semicomatose patients and using the scores of the survivors, the average improvement per patient in the placebo group was 21.4% (three deaths), whereas the average improvement per patient in the Decadron group was only 12.8% (four deaths).

There are several obvious differences between the two studies, which are deserving of comment. The criterion for admission to this study was a disturbance in level of consciousness, whereas this was not the case in Patten's study. Although the scoring systems are different, and no mention of level of consciousness is reported in Patten's study, the patients in our series were probably more severely ill. Unfortunately, of the eight semicomatose patients, all but two were randomized into the placebo series and, in a sense, were lost for statistical analysis. However, assuming that the patients in our series were more severely ill, it was in the more severely ill patients in Patten's group that the greater benefit of Decadron was demonstrated.

In our series the greater percentage of improvement occurred in the placebo group. The total dosage of Decadron differed in the two series. In Patten's study a total of 170 mg was given in the first ten days, followed by a "tapering" dosage for another seven days. In our series the total in the ten-day treatment period was 120 mg, with the tapering starting on the fourth day. One may argue that this dosage was insufficient, but even so it is still an acceptable dosage and as such it should have benefited some, whereas the converse was true.

The last patient scoring was 14 days in our study, whereas it was at 17 days in Patten's study. This three-day difference would not be expected to produce a significant change in patient scores.

Three patients with cerebral hemorrhage were included in Patten's study and all were in the placebo group. Two became worse and one

| TABLE 7 |
| Cerebral Infarction and CSF Pressure |
| Placebo | Decadron |
| Increased pressure, died prior to subsequent reading | 3 of 10 | 0 of 8 |
| Increased pressure, normal subsequent readings | 3 of 10 | 4 of 8 |
| Increased pressure, subsequent pressures increased | 4 of 10 | 4 of 8 |
| Normal pressure, died prior to subsequent reading | 5 of 16 | 2 of 20 |
| Normal pressure, normal subsequent readings | 7 of 16 | 14 of 20 |
| Normal pressure, subsequent pressures increased | 4 of 14 | 4 of 20 |
| Initial pressure over 180 mm H₂O | 10 of 26 | 8 of 28 |
| Total readings over 180 mm H₂O | 22 of 68 | 18 of 80 |
| Subsequent readings over 180 mm H₂O | 12 of 42 (28.5%) | 10 of 52 (19%) |
| Increased pressure, died within 14 days | 4 of 10 | 1 of 8 |
| Increased pressure, died later than 14 days | 3 of 9 | 4 of 8 |
| Normal pressure, died within 14 days | 5 of 16 | 4 of 10 |
| Normal pressure, died later than 14 days | 4 of 16 | 9 of 17 |
improved. If the patients with cerebral hemorrhage are excluded from the placebo group, the average worsening per patient is only 4.5% rather than 12%. Two of the patients with cerebral hemorrhage also had an initial score of over 25, so their exclusion in that portion of their analysis would certainly have a similar effect. No mention is made in their report about CSF criteria for inclusion or exclusion from the study.

**Summary**

Fifty-four patients with acute cerebral infarction were included in a double-blind study to evaluate Decadron as therapy. When comparison of patients with similar levels of consciousness was made, there did not appear to be any appreciable difference between the patients who received placebo therapy and those who received intravenous and intramuscular Decadron.

**References**


Dexamethasone as Treatment in Cerebrovascular Disease. 2. A Controlled Study in Acute Cerebral Infarction
RAYMOND B. BAUER and HENRY TELLEZ

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