Chronic cerebellar stimulation for cerebral palsy

Prospective and double-blind studies

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The effects of chronic electrical stimulation of the cerebellum in patients with cerebral palsy have been
studied using objective tests of joint compliance, and standardized assessments of developmental reflexes
and motor skills. Of 14 patients studied prospectively for 1 to 44 months, 11 showed improvement in motor
function. A double-blind test of 10 patients off and on stimulation for an average 8-week period showed no
significant changes. Thus, we have no proof that the functional improvements seen with long-term stimula-
tion are the result of cerebellar stimulation.

KEY WORDS • cerebellar stimulation • prospective study • double-blind study •
motor function • cerebral palsy

CHRONIC electrical stimulation of the cere-
bellum has been employed to reduce spastic-
ticity and improve motor function in patients
with cerebral palsy.1 Since Cooper1 introduced
the procedure 7 years ago, over a thousand patients have
had the operation. As with many new surgical
procedures, there has been considerable controversy
over its effectiveness. Some surgeons have reported
improvement in 95% to 98% of their patients, whereas
others have given up the procedure because they found
no beneficial effects.2,3 The only double-blind trial that
has been reported* used 24-hour periods on or off
stimulation, and no changes could be detected.4

After our initial experience with the procedure,
three points became clear. First, the patients and their
families uniformly endorsed the operation and
enthusiastically strived to improve motor function.
Second, the motor abilities of patients are often dif-
ficult to compare over many months and years, es-
pecially in young, growing patients. Third, the effects
of stimulation were reported by the families to last
days to weeks after the stimulation was stopped. This
means that any test of the efficacy of the procedure

*But see Addendum.
double-blind study does not give proof that the improvements are attributable to electrical stimulation.

Clinical Material and Methods

Patient Population

Fourteen patients with cerebral palsy were chosen for the prospective study according to the following criteria: hypertonia was present, which interfered with motor function; the patient was dependent in functional skills, including gait; and the patient had normal or nearly normal intelligence. They ranged in age from 6 to 30 years. All patients had received extensive physical therapy and speech therapy (as appropriate), and they had failed to demonstrate significant changes in the recent past. Their motor disorders were classified as spastic (six patients), spastic athetoid (four patients), and dystonic athetoid (four patients) (Table 1).

Ten patients volunteered for the double-blind study; seven of the 14 patients from the prospective group and three patients with electrodes implanted at another medical center. Seven patients studied prospectively were unable to cooperate in the double-blind study because they lived too far from the medical center or because of difficulty coordinating the testing with school or work.

Test Protocol

In both studies the patients received stimulation for 1 to 44 months, during which the stimulation parameters were varied in an effort to maximize function. For the prospective study, results were compared between tests taken preoperatively and at the beginning of the double-blind study. If the patients were not included in the double-blind testing, preoperative results were contrasted with those following the longest period of stimulation. The double-blind study was divided into two periods of approximately 8 weeks each. (At the family's request, one patient was tested at 3-week intervals and another at 12-week intervals). The evaluations were conducted just before the beginning of the first blind period and at the conclusion of each blind period. The patients were either on or off stimulation in randomized sequence, that is, on-off, off-on, on-off, off-on, with the "on" period providing cerebellar stimulation at levels that had previously been established as optimum for that patient.

Equipment

Thirteen of the 14 patients of the prospective study and seven patients studied in double-blind fashion had an eight-electrode array placed on the superior cerebellar hemispheres; two sets of four-in-line, alternate polarity, disc electrodes were supported by a Silastic pad and connected to a single receiver. The other three patients from the double-blind study had a 32-electrode configuration with a double row of four-in-line, alternate polarity, platinum-disc electrodes contained in a single Silastic pad; one pad was placed over the superior and posterior surfaces of each cerebellar hemisphere. The electrode arrays from the left and right hemispheres were connected to separate receivers placed in the infraclavicular space. The remaining patient in the prospective study had a combination of electrode arrays; one array was in the superior-posterior configuration and the other on the superior surface only (Case 6, Table 1).

Patients received 8 to 12 hours of stimulation per day in an on-off pattern ranging from 1 to 20 minutes. The pulse width was 0.5 msec. With intraoperative measurements of electrode impedance of 300 to 600 ohms and voltages of 1 to 4 volts, the peak currents were calculated to be 1.67 to 13.33 mA (0.05 to 0.41 mA/sq mm for the eight-electrode design, 0.01 to 0.10 mA/sq mm for the 32-electrode system, and 0.026 to 0.208 mA/sq mm for the superior-posterior array).

Evaluation Procedures

The same tests were performed in both the prospective and double-blind studies, and the same investigators tested all patients in all phases of the studies. The standardized Milani-Comparetti scale was employed to rate developmental reflexes and motor skills. Reflex assessments were made according to the presence or absence of primitive reflexes (that is, Moro, tonic neck, and grasp reflexes) and mature responses (that is, Landau, parachute, and tilting reactions). Functional skills that were graded included head and trunk control in various positions, balance, and mobility, including gait. When appropriate, the Denver Developmental Screening Test was used to evaluate fine motor skills.

Motor control studies were performed on each patient to determine joint compliance at the ankle. Compliance measures could not be made on three patients with dystonic athetosis, due to the extreme range and variability of their hypertonia and hypotonia. Furthermore, in the prospective study, two patients were not tested because the computer running the testing failed.

The testing apparatus for measuring joint compliance has been described previously. The patients were comfortably seated in a chair with one foot strapped to a footplate which rotated about an axis through the medial malleolus to permit dorsal and plantar flexion. The computer directed randomized 11-second periods of oscillations of the footplate at 12 frequencies ranging from 3 through 12 Hz. Calculations were made of joint compliance from the constant torque input and the varied output of joint angle; the compliance was plotted for each frequency of oscillation. Visual comparisons of joint compliance between test periods were made according to the changes in resonant frequency, that is, the frequency at which the maximum angular displacement oc-
FIG. 1. Results in the prospective study. Changes in joint compliance, developmental reflexes, and functional skills in 14 patients with chronic electrical stimulation of the cerebellum. The type of cerebral palsy is denoted as follows: dots indicate spastic patients, cross-hatching indicates spastic athetoid, and single-hatching dystonic athetoid.

FIG. 2. Results of a double-blind study of 10 patients on and off stimulation for two 8-week periods. The patients could frequently identify if the stimulation was on or off, but no significant changes in joint compliance, developmental reflexes, or functional skills were seen. The type of cerebral palsy is indicated as in Fig. 1.

that the stimulation had been "on" or "off" during the previous blind period, and the basis for making that determination.

Data Analysis

In the double-blind study, our primary concern was to show any changes due to cerebellar stimulation, so we have used a simple scoring system for the results which gives points for any change found on a test regardless of the degree. The baseline on stimulation and the end of the first test period were compared, and then the end of the first and second test periods was compared. If an appropriate change took place, one point was given. For example, if an "on" period was followed by an "off" period, and the patient became worse functionally, +1 was given. If he stayed the same or improved, −1 was awarded. In the judgment as to whether the stimulation was on, no point was given if the patient was uncertain. Also, no point was given in the developmental reflex testing if one reflex improved and another worsened.

Results

The results of the prospective study of the 14 patients who had 1 to 44 months of stimulation are listed in Table 1. The primitive reflex testing showed nine patients improved (64%), four were unchanged, and one regressed. Compliance measures on nine of 14 patients who were able to be tested indicated that five (56%) had more relaxation of their triceps surae and anterior tibial muscle groups, two had no change, and two were more stiff. Most significantly, 11 of the 14 patients (79%) were better functionally, none were worse, and three were unchanged. A majority of the gains were small and consisted of improved sitting balance and better head control. A few improvements were more important for overall motor control, such as one patient who was able to crawl on all fours, one who could get up stairs with a side rail, and one patient who had no further need of a wheelchair.

To see if the type of cerebral palsy related to improvement in compliance, reflexes, or motor control, each group was compared, but no significant correlations were found. This is illustrated in Fig. 1, which shows relatively even distributions of each type of motor disability.

Double-blind results are displayed in Fig. 2. The scores for primitive reflex testing, compliance, and motor function showed no relationship to the change in stimulation status. On the other hand, many of the patients could identify correctly if the stimulator was on or off. For this one test the overall score was 9, and six of the 10 patients were correct both times. When asked how they judged that the stimulator was on, the patients usually stated they felt "more relaxed." None felt any pain, headache, or tingling, which is occasionally reported with current spread to the tentorium.
Chronic cerebellar stimulation for cerebral palsy

TABLE 1
Results of a prospective study in 14 patients with cerebellar stimulation for cerebral palsy*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Implant (yrs)</th>
<th>Duration of Stimulation (mos)</th>
<th>Joint Compliance</th>
<th>Primitive Reflexes†</th>
<th>Developmental Reflexes</th>
<th>Function</th>
<th>Score</th>
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<td>spastic</td>
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<td>+ ATNR</td>
<td>- tilting reaction</td>
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*Summary of results: The 14 patients ranged in age from 6 to 30 years. Five of nine patients so tested (56%) had improved joint compliance; nine of the 14 patients (64%) had improved developmental reflexes; 11 of the 14 patients (79%) had improved function.

†ATNR = asymmetrical tonic neck reflex. STNR = symmetrical tonic neck reflex. Lost = -- and Gained = +.

§These seven patients were also included in the double-blind study.

| No change = 0, overall improvement = +, overall deterioration = —.

Another way of reviewing the data is to ask if any of the patients changed appropriately in all the measures. If the changes were random, independent, and equally probable, then the odds for a perfect score for any given patient would be 2⁸, or 1 in 256. One patient had such a record.

As the figures again illustrate, no relationship between the test results and the type of cerebral palsy was found in this small group of patients.

Discussion

The findings of the prospective part of this study are similar to the largest reported series of Cooper.1 About two-thirds of the patients had some observable functional improvement, but only a few were helped significantly in terms of greater self-sufficiency and motor function. Objective tests of rigidity and developmental reflexes also demonstrate changes. These findings suggest that the reduction of rigidity and loss of primitive reflexes and the acquisition of more advanced responses contribute in part to the functional gains. The relationship between function, rigidity, and reflexes is, however, complex, and improvement in one does not always mean an advance in another. The prospective results do indicate why many patients and their families consider the operation effective. Although the gains are small, they are often important to these seriously impaired patients. None of our 14 patients has stopped using cerebellar stimulation, including those in whom we could measure no functional changes.

To our surprise, the degree of functional improvement did not correlate well with the type of motor dis-
order. We had expected the patients with rigidity as their dominant clinical finding to show the greatest gains, a decrease in tone being necessary for successful performance. In fact, the initial rigidity or the amount of change in limb compliance did not relate to functional gains. Part of the lack of correlation may be due to the small size of the different patient groups and the differences between individual patients within a group.

A second possibility is that muscle tone itself is not a good indicator of function. In a previous electrophysiological study, we demonstrated that the degree of co-contraction of opposing muscle groups, not general tone, was related to the inability to move the forearm in a tracking test. In fact, patients sometimes rely on increased tone for certain movements. An example is the use of excessive extensor tone in the limbs to provide support in crutch walking and transfers.

The double-blind results throw into question whether cerebellar stimulation itself was the cause of the patients' improvement. The one patient of 10 who changed appropriately on all the trials may be an example of a true effect of stimulation, but the sample size is too small to be sure. The overwhelming evidence is that, for most of the patients, the withdrawal of stimulation for 2 months did not reverse the changes seen on the prospective study. On the other hand, many of the patients were able to identify if the stimulator was on or off. If, as they sometimes stated, a "feeling of relaxation" was the clue to stimulation, our tests of passive joint compliance were not subtle enough to detect it.

The fact that many of the patients could correctly tell if the stimulation was on or off means that, although we used a double-blind protocol, the testing from the point of view of at least six of the 10 patients was not "blind." This knowledge did not seem to influence the results of our tests of joint compliance, developmental reflexes, or function. No significant changes with the status of stimulation were found for either those six patients or the other four. Knowing the stimulator was on did not improve performance.

How can the advances on the prospective study be explained? If the cerebellar stimulation itself has no discernible effect, then perhaps the whole procedure, the high expectations of the patients and their families, and the new treatment environment have created improved motor control. Although the neuropathological lesions that underlie cerebral palsy are fixed, the clinical manifestations may vary over time. We have seen a number of patients definitely improved even though their stimulator was found to be broken when it was checked. One of the double-blind patients was off stimulation during both testing periods yet continued to improve in gait.

An alternative way of evaluating the findings of the double-blind study is to say that the effects of cerebellar stimulation are not reversible or take much more time to reverse than we allowed. Our experimental design cannot exclude this possibility. We chose 8-week periods for the testing because a short trial of 1 day on and off had shown no changes, and our patients indicated that they could feel changes in a few days to at most 2 weeks if stimulation was interrupted. About 8 weeks, therefore, seemed a reasonable minimum trial period. Much longer would have been difficult for the patient and would have involved major changes in routine, such as returning to school or sheltered workshops. We also found it necessary to establish before the testing period the stimulation parameters that benefited the patient. There is some disagreement about what frequency and current density is best, and we did not want to prejudge the issue. Some of our patients reported no effect or worsening of symptoms with certain voltages and frequency settings. If the period of stimulation before the double-blind test caused permanent changes in motor function, our scoring system would be inappropriate. In support of this possibility, of the 20 tests performed on the double-blind patients, motor function was the same or improved in 19, and only once did function worsen. It can be argued that this shows that the patients had reached a plateau, and no further gains could be expected.

An equally important point is that the operation that we are studying is far from perfected. In animals, differences in electrode placement, stimulation rates, and current densities greatly affect the motor responses. There is no need to believe that the present electrode systems are the best possible, and work is in progress to modify the procedure. Another factor in the response in patients may well be the various neurological lesions of cerebral palsy patients. Clearly, spastic, athetoid, and dystonic patients have very different motor system problems, and the neurophysiology of these abnormalities is little studied and poorly understood. Unfortunately, our small sample size does not give a clue as to who will respond the most. A much larger series of patients will have to be studied, which is a possibility since over a thousand operations have been performed in this country. It would be unfortunate if our limited double-blind results from such a small number of patients were taken as a reason to stop all work on the operation. We are only beginning to explore the new technologies of neurostimulation for motor disorders, and even modest gains for cerebral palsy patients would be significant. For the moment, however, the operation cannot be recommended for widespread use. Until a controlled study shows an unequivocal difference attributable to cerebellar stimulation, and that such gains are significant in improving the patient's life, the procedure should be considered on trial.

Addendum

Since the submission of this prospective and double-blind study on cerebellar stimulation, Whittaker's similar study has appeared (Whittaker CK: Cerebellar...
stimulation for cerebral palsy. *J Neurosurg* 52: 648–653, 1980). His conclusions are basically the same as ours, namely, that after a period of stimulation, ranging from several months to years, skilled observers cannot find any functional difference between periods on and off stimulation for the test group as a whole. One is therefore tempted to draw the further conclusion that the operation is a sham and that the effects are totally those of an expensive placebo. Bucy has implied this recently in his comments on the procedure (Bucy PC: Cerebellar stimulation. *Surg Neurol* 13:124, 1980, Editorial). We do not believe that this attitude is justified by Whittaker’s or our study. First, good evidence exists that cerebellar stimulation has definite physiological effects: for example, on muscle rigidity and segmental reflexes (see references 9 and 10, and Fisher MA, Penn RD: Evidence for changes in segmental motoneurone pools by chronic cerebellar stimulation and its clinical significance. *J Neurol Neurosurg Psychiatry* 41:630–635, 1978) and on coordination of breathing (Wong PKH, Hoffman HJ, Froese AB, et al: Cerebellar stimulation in the management of cerebral palsy: clinical and physiological studies. *Neurosurgery* 5:217–224, 1979). These physiological changes were found in only some of the patients tested and, of course, the patients with the greatest changes were used to illustrate the point. The problem is that many patients do not show these changes, and, even if found, the changes do not necessarily translate into clinical functional gains.

The second reason we think that the operation is not a pure placebo is that we found one patient who responded correctly on all the tests on and off stimulation. For this patient, we have to conclude that cerebellar stimulation has an effect on rigidity, developmental reflexes, and function, and the patient could sense this. With our method of analysis, other patients who changed on only some of the tests would have been considered to have no detectable changes. One wonders if similar patients could be found in Whittaker’s study, such as Cases 1, 2, and 5. By looking at the whole, a few true examples of effectiveness may be missed with the design used. Of course, no definite changes for the group as a whole were found on our and Whittaker’s studies, which is the major conclusion.

The overall functional results must be our main concern when recommending an operation, and there is no unequivocal evidence that cerebellar stimulation is effective. Prospective studies without double-blind testing cannot be relied upon because placebo effects cannot be sorted out from real ones. On the other hand, there is enough evidence that some patients have true physiological changes and possibly functional gains, so that investigation of the procedure either to characterize the patients who do change or to improve the operation is justified on a limited basis.

References


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