Experimental Treatments of Acute Spinal Cord Injury

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ALTHOUGH physicians have a choice of treating acute injuries of the spinal cord by realignment of the spinal column, surgical decompression, or measures that alter neuronal metabolism and prevent or reduce edema of the cord, or by combinations of these methods, the relative merits of these procedures appear to be unknown because they have not been evaluated comparatively. There is no known experimental model to assess bony alignment, but Freeman and Wright have described an experimental spinal cord concussion-contusion in which sufficient threshold trauma produces at least a moderately prolonged paraplegia and possibly a lasting neurological deficit and by which the relative efficacy of most current treatments could be compared. Using a similar experimental model, we evaluated standard dural decompression, direct local cord hypothermia, intramuscular dexamethasone, and intrathecal methylprednisolone.

Materials and Methods

We used beagle dogs† raised specifically for research; all were young and weighed 8.4 to 15 kg. Most of the animals weighed approximately 12 kg and were female. They were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Endotracheal tubes were placed in all the dogs, but assisted respiration was not required. Following the usual aseptic technique, a midline longitudinal incision was utilized to remove the posterior laminae of the tenth, eleventh, and twelfth dorsal vertebrae completely. The epidural fat was removed, but the dura was not opened.

Received for publication June 21, 1968.

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† The principles of laboratory animal care as promulgated by the National Society for Medical Research were observed.

The trauma was inflicted by striking the dura-covered cord with an impounder from a 25-gm weight dropped 15 cm. Thus, a 375-gm-centimeter force was delivered, which represented the minimal trauma (threshold) at which a physiological transection of the cord might be expected.10

All animals remained under anesthesia and were started on the respective treatments 3 hours after the trauma. Forty-eight (48) beagles were divided at random into four groups of 12 animals.

Group 1 (4 males, 8 females). In this control group, the dura was opened over the area of trauma and over the next dorsal and ventral segments if the spinal cord. Gelfoam was placed over the dural decompression; the paravertebral musculature, fascia, and skin were closed in layers and the wound dressed.

Group 2 (3 males, 9 females). These animals received local hypothermia as described by Albin, et al.,1 for 3 hours beginning 3 hours after injury. The dura was opened and tacked laterally to the paravertebral musculature during the treatment. Hypothermia was effected by irrigating the wound with saline circulated through tubing in an ice-water bath at 0°C at a rate of 75 to 100 ml/min. Temperature was recorded from the saline irrigation, the spinal cord, and the deep musculature 4 to 5 cm lateral to the operative site by No. 26 needle thermisters connected to the Tele-Thermometer.§ The temperature of the saline irrigation was always kept below 4°C. At the end of the period of cooling, the tacking sutures were cut, but the dura, which then assumed a more normal position, was not closed by suture. Gelfoam again was placed over the dural incision, and the wound closed in layers.

Group 3 (2 males, 10 females). These animals were treated with intramuscular injec-

§ Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio.
tions of gluco-corticoid steroids starting 3 hours after injury, after which the wounds were closed without opening the dura. The dose of dexamethasone was 0.50 mg/kg/24 hours on the day of trauma and 0.24 mg/kg/24 hours on the first postoperative day, given in divided doses, after which the medication was changed to methylprednisolone 1.3 mg/kg/24 hours, given as a single dose for 7 days.

Group 4 (2 males, 10 females). In this group the dura was not opened but each beagle received a single dose of methylprednisolone 8 mg/kg delivered intrathecally under direct vision directly at the site of trauma with a small curved 25-gauge needle. Thereafter the wound was closed.

Postoperatively, the animals were kept in a recovery unit for 24 hours and then transferred to cages with straw-covered bottoms for further care and evaluation. If the animals were completely paraplegic, their bladders were emptied frequently by expression during the first week after injury. The beagles were retained 5 to 6 weeks under the care and surveillance of veterinarians and the authors. The end point for results was a plateau of the neurological status for 4 to 6 weeks after injury.

Neurological Evaluation. To obtain objective results, only the post-trauma neurological status was judged on motor function. Sensory examination (pain perception) produced similar results not considered objective and, in addition, was poorly received by the animals. To perform effective repeated evaluations, we wished to remain on as friendly terms as possible with these animals. The end point of motor recovery was based on the degree of recovery 4 to 6 weeks after the laminectomy and trauma, after which time the animals made only very slow further recovery. Grading of the neurological status was based in part on the scale of function described by Tarlov: 1) complete paraplegia, no voluntary movements; 2) perceptible movements of joints, minimal voluntary movements; 3) good movements of joints, able to right and stand, but not run; 4) ability to stand and walk with some spastic running; and 5) running with little deficit and with a near complete recovery. The animals’ functional status was judged without knowledge of the treatment groups. Three identical scores in succession and all within the final week were considered as an end point; examples were recorded on movie films.

The animals were then given a fatal dose of pentobarbital, and the spinal column for two segments on each side of the injury was resected and placed in buffered formalin. After the tissues had fixed for 1 week, the spinal cord was removed, and histologic sections taken proximal and distal to the lesion as well as through it were stained with hematoxylin and eosin. Special stains for myelin were performed on occasion.

Results

Figure 1 shows the variation in final recovery. Nearly 90% of the animals achieved stable neurological status within the first 2 weeks after injury, but about 10% required 4 to 5 weeks for stabilization. The average grade of functional recovery is recorded in Table 1.

Control Group. The control group reached an average functional level of 2.1 in which the animals had minimal but definitely perceptible voluntary movements of the joint. These animals were anesthetic to pain in their hind legs and generally had a spastic bladder. Three animals spontaneously recovered to a level of 4 with ability to stand and walk with poorly coordinated spastic running, but the fact that one animal died and five others remained paraplegic indicates that the outlook of half of these animals was very poor. The animal that died, one of the few male dogs used in the experiment, developed uncontrolled spastic reflex penile erections and urological infection, and succumbed to bacteremia and septicemia caused by a Pseudomonas organism which was resistant to routine antibiotics.

Treated Groups. Distinctly different from the controls were the treated groups. Four animals in Group 2 (treated by local hypothermia) and four animals in Group 3 (intramuscular dexamethasone) recovered nearly completely. The average grade of functional recovery for those receiving local hypothermia was 3.5, and for those receiving intramuscular dexamethasone was 3.3. These results were significantly different from that of the controls (p < 0.01). This grade of motor function meant that the ani-
mals could move their hind legs, right themselves, and stand; many of the animals could run, though spastic. Their sensory and functional urological deficits were less pronounced.

A noteworthy observation in the local hypothermia group was that while the animals were being treated the spinal cord appeared smaller and less edematous. Exact measurements were not made.

The animals in Group 4 (treated with intrathecal depomethylprednisolone) did nearly as well, by achieving an average functional grade of 2.9, which also was significantly different from that of the controls (p < 0.05).

In these treated groups a few animals also remained paraplegic, and two died. One animal in the local hypothermia group died early in the first postoperative week from unsuspected pneumonia, and one male animal in the intrathecal depomethylprednisolone group had an uncontrolled urinary tract infection.

**Pathological Studies.** Gross pathological studies were not helpful, but microscopic examination showed a correlation between neurological function and the appearance of the spinal cord. Vacuole formation and glial proliferation infiltrated the normal architecture in the animals with the greater neurological deficits and consequently in the more severely injured cords. With these changes, there was a loss of myelinated fibers; although the grade of recovery correlated with pathology, there were no distinct histological differences in the various treatment groups. A suggestion of greater internuncial neuronal loss in animals treated with direct cord hypothermia could not always be substantiated.

**Discussion**

The experimental model in these studies is critical to the accurate evaluation of these data and to its potential clinical application. Basically, the 375-gm-centimeter force represents the threshold trauma necessary to produce complete and prolonged paraplegia in one-half of the animals and serious neurological deficits in the remaining half. A 400-gm-centimeter force causes a complete paraplegia in almost 100% of dogs. This impact is equivalent to a firm tap by one's index finger. Forces greater than 450 to 500 gm-centimeter result in extensive mechanical damage that precludes any type of treatment. Thus, the number of clinical cases that would sustain equivalent trauma

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**TABLE 1**

*Average grade of functional recovery for four groups of beagles*

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Treatment</th>
<th>Grade of Recovery*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Controls, standard</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>Local hypothermia</td>
<td>3.5 (p&lt;0.01)</td>
</tr>
<tr>
<td>3</td>
<td>Intramuscular dexamethasone</td>
<td>3.3 (p&lt;0.01)</td>
</tr>
<tr>
<td>4</td>
<td>Intrathecal depomethyl-</td>
<td>2.9 (p&lt;0.05)</td>
</tr>
</tbody>
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* The probability value is based on a paired "t" test with each group compared to the controls.
are indeed few, but if one is dealing with that rare lesion, these studies are pertinent.

The dog is moderately high on the phylogenetic scale but certainly is not as preferred as the chimpanzee or the baboon for studies on the central nervous system. But a large number of animals is required for this kind of study. We were able to obtain beagles that had been raised for research, were of uniform size and age, could be matched in groups of four, and thus satisfied the requirements of a paired "t" test in the statistical analysis. Thus, with only 12 animals in each group, we obtained statistically significant results for local hypothermia and intramuscular dexamethasone.

Trauma inflicted at the thoraco-lumbar junction in the dog, which has a spinal cord that extends to its seventh lumbar vertebra, is better equated to the level of the ninth dorsal spine in man. Even with these limitations in applying to man the results obtained from dogs, the primary goal of comparing various modalities of treatment in spinal cord injury in uniform preparation may be achieved.

With this experimental model, local hypothermia or large doses of intramuscular steroids result in better neurological function in the immediate postoperative period than that achieved in the control group treated by standard decompression. The response of the spinal cord to trauma includes self-destructive swelling and edema. Prevention of this aspect of the pathophysiologic response minimizes the clinical deficit and the pathological changes in the cord. Additional studies support this thesis. The swelling and edema promote impaired circulation in already embarrassed tissue and lead to irreversible changes in those tracts of fibers which cross the lesion. Incomplete lesions or threshold trauma would benefit by preventing a self-destructive pathophysiological process like swelling and edema. Thus, if there is no evidence of spinal cord compression by extraneous material, therapy should be directed at preventing the edema rather than at decompression.

Both local hypothermia and intramuscular steroids were useful; although these two groups differed significantly from the controls, they were not significantly different from one another.

Local Hypothermia. Local hypothermia appeared to achieve slightly better results than intramuscular steroids but it was associated with one postoperative death from pneumonia. However, its use requires a large expenditure of time, personnel, and equipment; it also may damage certain structures of the cord. The last point is raised because Negrin successfully used local cord hypothermia to relieve muscle spasticity in multiple sclerosis and postulated that the mechanism of action in this therapy is destruction of parts of the spinal tracts serving the gamma motor system or the internuncial neurons. Although the pathological studies of the cords of our animals did not substantiate any fiber or internuncial neuronal loss over and above that caused by trauma, anatomical structures could not have been added to those patients described by Negrin, and it is assumed that something was destroyed. Thus, although local hypothermia gave the best results, and even though we did confirm the studies by Albin, et al., and would encourage further studies in this field, we are reluctant to advocate its use because of the forenamed objections.

Glucocorticoid Steroids. Improved functional status was gained with glucocorticoid steroids without the difficulties associated with local cord hypothermia. However, this is no panacea either, for in our clinical trials we did observe gastro-intestinal hemorrhage in one patient who was receiving this drug. The difference in the utilization of time and personnel is marked, and it is probably the treatment of choice in the acute spinal cord injury. For the last 4 to 5 years, steroids have been used extensively for intracranial disorders of the central nervous system. This medication is known to maintain the cellular membrane and the lysosomes in states of inadequate circulation and inflammation. With this background, it would appear that cautious use of a glucocorticoid steroid deserves consideration in the treatment of acute spinal cord trauma. The dosage in these experiments translated to an average-sized man implies 6 mg every 4 hours on the day of injury followed by the standard 4 mg every 6 hours for a few days thereafter.

Intrathecal Depomethylprednisolone. This medication also improved the neurological
function over that of the controls but not nearly as significantly as the intramuscular steroids. This observation implies that the glucocorticoids are required in the systemic circulation as well as in the local tissues. Systemic steroids are known to have profound influences in maintaining vascular integrity, and it is this vascular support to the cord that may account for the difference between the two groups of animals. An alternative conclusion is that the difference is simply dependent on the total amount of glucocorticoids. Combination therapies should be considered both for experimental and clinical evaluations, especially when an incomplete and/or threshold traumatic lesion is found or suspected.

Summary

Decompression (control), local cord hypothermia, intramuscular dexamethasone, and intrathecal depomethylprednisolone, each started 3 hours after injury, were compared in four groups of dogs subjected to a standard experimental trauma to the spinal cord known to produce prolonged paraplegia in one-half of the animals. Statistically significant improvement and recovery of neurological function resulted from the use of intramuscular dexamethasone or local hypothermia to the cord. The advantages and disadvantages of these two methods of treatment have been discussed.

With a threshold concussion-contusion of the spinal cord, the pathophysiological process includes swelling and edema formation which result in further destruction to the transversing fiber tracts. Prevention of this self-destructive edema and swelling in experimental cord contusion helps maintain neurological function. With the exception of certain medical centers set up to properly administer and to follow local hypothermic treatment of spinal cord patients, dexamethasone medication is recommended for acute spinal cord injury when there is no persistent anatomical compression of the cord and especially when an incomplete or threshold traumatic lesion is found or suspected.

References