Title: Surgical Neurology
Volume: 10
Issue: 1
Year: 1978
Month: Jul
Pages: 71-76

Article Title: Experimental spinal cord trauma, III: Therapeutic effect of immobilization and pharmacologic agents

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Printed: 2/5/2013 9:26:39 AM
Experimental Spinal Cord Trauma, III: Therapeutic Effect of Immobilization and Pharmacologic Agents

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A wide variety of pharmacologic agents has been suggested to serve as therapeutic adjuncts in the management of acute spinal cord trauma. The present study was conducted to determine what effect, if any, these agents have when they are added to immobilization of the spinal column, the most widely used clinical measure. Rhesus monkeys were subjected to different levels of experimental spinal cord injury with and without subsequent immobilization by means of a figure of eight ligature. In the control group, five of six animals impacted at 500 gm-cm were paraplegic. In the immobilized animals, three of four animals impacted at 500 gm-cm recovered completely and the fourth was only mildly paraparetic. Paraplegia could not be uniformly produced in this group until 800 gm-cm forces were routinely employed. In the second phase of the study, only immobilized animals were used, with and without drug therapy. No change in the force-injury curve, above and beyond that from immobilization, can be demonstrated for monkeys given dextran, phenobarbital, methyldopa, phenoxybenzamine or vasopressors. The pathophysiologic concepts upon which such agents are advocated should be reassessed. Spinal immobilization can significantly improve the clinical outcome following experimental spinal cord injury; it may also serve to control some of the variability previously observed in pharmacologic experiments.

Many therapies have been studied in the hope of retarding or reversing the pathologic events that are recorded following spinal cord injury. These pathologic changes most often include central hemorrhagic lesions, primarily involving the gray matter with progressive necrosis and marked edematous change in the white matter. If they are allowed to progress far enough, they render the cord segment totally useless. Various drug or medical regimens, such as blockage of central bioamine buildup, restoration of depressed blood flow, depletion of vascular bioamines, depression of metabolism, maintenance of perfusion pressure, etc., have been advocated to stop or retard the pathophysiologic process.

New therapeutic approaches are usually tested in Rhesus monkeys subjected to posteriorly directed experimental spinal cord injury. A 500 gm-cm (a 50 gm weight dropped 10 cm) impact at T-11/T-12 consistently produces clinical paraplegia in these animals. Monkeys impacted at 400 gram-cm (a 50 gram weight dropped 8 cm) demonstrate variable but immediate deficits. One such animal suffered a delayed deterioration, two days after injury, and was observed to have a dislocation and severance of the spinal cord at the interspace beneath the laminectomy site. To prevent this from happening in the future, a technique of vertebral immobilization was instituted. Follow-up studies revealed that 500 gm-cm contusions would not produce paraplegia in animals surgically immobilized following injury.

As a result, we have tested the therapeutic effectiveness of alpha-
methyldopa, dextran, phenoxybenzamine, phenobarbital and vasoressors in animals partially protected by immobilization. In the context of our experimental paradigm, these agents do not offer any therapeutic advantage beyond the use of immobilization alone.

Methods

In the first phase of this study, 32 Rhesus monkeys were subjected to a variable degree of spinal cord contusion at the T-11/T-12 level. The control group consisted of 19 animals; injury was inflicted with up to 500 gram-cm but without vertebral immobilization. The experimental group received injuries from forces in the 500-800 gram-cm range and rigid vertebral immobilization followed impaction in every case. There were 13 animals in this group.

Each animal was anesthetized with Surital-R (Sodium Thiopental), 15-20 mg/kg and Serynalan-R (Phencyclidine hydrochloride) 1-2 mg/kg. After sterile preparation, a T-11/T-12 laminectomy was performed and the cord with the dura intact was exposed. In the immobilized group, bone removal was limited to only one vertebra. A 50 gram weight was dropped through a measured tube so that a calculated injury could be inflicted as desired. For example, 50 grams dropped through 10 cm of tubing equals a 500 gram-cm injury; 50 grams dropped 12 cm equals a 600 gram-cm injury, etc. A lightweight plastic impounder was placed in the tube and rested on the dura-covered cord. Thus the falling weight did not make direct contact with the cord and the injury force was transmitted through the plastic device, whose area of impact measured 45 mm.²

The height from which the 50 gram weight was dropped was progressively increased until clinical paraplegia was consistently produced in the experimental group. In the 13 immobilized animals, immediately following injury, a figure-of-eight #5 silk suture was placed such that it bridged the laminctomity site with superior and inferior loops of the figure attached to the respective posterior spinous processes. The suture achieved mild extension with relaxation and immobilization of the spinal cord in the area of injury. The wound was then closed in standard fashion.

Clinical neurological evaluation of the animal was made at six hours, and on each day for seven days. The usual system for motor assessment was implemented: no voluntary movement (Grade 0), trace movement (Grade 1), definite movement of joints but could not run (Grade 3), or the animals walked and ran normally (Grade 4).

In the second phase of the study, a total of 50 male Rhesus monkeys were used. Thirty were subjected to experimental drug therapy and 20 acted as further controls. The traumatic force ranged from 500-800 gram-cm with 800 gram-cm producing complete paraplegia in all control animals. All animals in both groups received mechanical immobilization by the method described above, employing a #8 silk suture.

In the experimental group, drug therapy was initiated one hour after the infliction of trauma. All animals received phencyclidine, as necessary, to keep them free of pain. With the exception of the Dextran studies, all drug treated and control monkeys received a constant infusion of normal saline containing 5% glucose at a rate equal to 50 ml/kg/hr. This infusion was maintained for 36 hours.

Dextran studies: Eight animals received intravenous infusions of Dextran containing 5% glucose at an infusion rate equal to 50 ml/kg/24 hr.

Phenobarbital studies: In addition to an IV infusion of saline and glucose, five animals received intravenous phenobarbital. This was given as a dose of 25 mg/kg at one and five hours post-trauma, then five additional doses of 12.5 mg/kg were given at four-hour intervals for a total dose of 112.5 mg/kg during...
Results

Immobilization vs. non-immobilization: In the control group, six out of seven animals injured by a 200-300 gram-cm force were completely normal. Only one had any weakness—a mild paresis. All five animals injured at 400 gram-cm demonstrated weakness in their lower extremities. Five out of six animals in this control group who received a 500 gram-cm injury were paraplegic (Grade 0-1). The sixth animal at 500 gram-cm had significant movement of the lower extremities, but could not walk or stand (Grade 2). This biological response curve is presented in Figure 1.

One animal that sustained a 400 gram-cm injury was able to stand in his cage the day after operation. The next day, he was noted to be less active and demonstrated poor movement of the legs (Grade 1). On the third day, he was completely paraplegic (Fig. 2). After remaining paralyzed for the rest of the week, he was sacrificed. At autopsy, the vertebra had completely dislocated and the spinal cord was severed. To prevent this from happening again, the immobilization procedure was instituted.

Three of four experimental immobilized animals receiving a 500 gram-cm injury were graded normal (Grade 4) and one was Grade 3. One animal received a 600 gram-cm injury and was Grade 3. Two animals received a 700 gram-cm injury and they were Grade 3. Two animals received a 750 gram-cm injury and were given a grading of 0 and 1. Four animals received a 800 gram-cm injury with subsequent grading 0. These results are presented in Figures 3 and 4.

Immobilization with and without drug treatment: With the initiation of immobilization of the vertebra in and about the site of the injured spinal cord, we were able to obtain a new pathophysiologic biologic control curve (Fig. 5). The immobilization assured us that the monkeys could not mechanically add more injury to the cord than we had inflicted. Changes in the expected clinical course would then presumably reflect the addition of a given drug to the therapeutic regimen. It was not until 800 gram-cm of force was used that a significant number of animals could be rendered paraplegic (Grade 0-1).

Results from the monkeys treated with Aldomet (Fig. 6) show that two monkeys who were given 500 gram-cm of trauma received normal grades of 4. Three of the monkeys received 750 gram-cm of trauma: one achieved a grade of 3 and the other two were totally paraplegic (Grade 0). The three animals who received 800 gram-cm of trauma were all

The 36-hour treatment period.

Methyldopa (Aldomet) studies: Eight animals received constant infusions of saline and glucose containing methyldopa, prepared such that 30 mg/kg was administered during the first treatment hour followed by 20 mg/kg/hr for the remaining 35 hours of the treatment period. The total dosage of methyldopa administered was 750 mg/kg.

Phenoxybenzamine (Dibenzyline) studies: Six monkeys were treated with phenoxybenzamine by administering 5 mg/kg one hour post-trauma followed by 2.5 mg/kg every six hours for a total dosage of 20 mg/kg during the 36-hour treatment period.

Vaspressor studies: Two animals were treated with norepinephrine (Levophed) and one animal received epinephrine (Adrenalin). The initial infusion rate was adjusted so that 0.5 mg/kg/min was administered. Efforts to maintain blood pressure with these or higher doses often failed. While initially pressure was maintained, in time fell to approximately 20 mm Hg below pretrauma level.

Clinical neurological examinations were then performed each day for one week, utilizing the previously described grading system. On the seventh day all animals were sacrificed for pathologic study.
paraplegic. Thus, there appears to be no significant difference between the controls in this phase of the study and the Aldomet treated monkeys.

Two monkeys were given 500 gram-cm of trauma and received Dextran; they achieved clinical Grade 4. Three animals who received 750 gram-cm of trauma were rendered totally paraplegic (Grade 0) as were three other monkeys receiving 800 gram-cm force (Fig. 7). Again, the Dextran treated monkeys showed no significant variation from the controlled group.

The results of the monkeys treated with phenoxylbenzamine can be seen in Figure 8. Note that in the two animals who received 500 gram-cm of trauma, one received a normal grade of 4 and the other was totally paraplegic (Grade 0) and died on day 4. It is possible that the drug contributed to the animal’s demise. Two more monkeys tested at 750 gram-cm of force were rendered totally paraplegic as were two treated at 800 gram-cm of force. Testing with this drug was discontinued because the investigators were convinced that the drug was more detrimental than beneficial.

All of the barbiturate treated monkeys remained totally paraplegic (Grade 0). Of this group, two monkeys received 750 gram-cm of force and three received 800 gram-cm. Although the monkeys were not tested at 500 gram-cm of force, the results indicated that they did not differ significantly from the controls (Fig. 9).

In an effort to increase the blood pressure in the injured monkeys, we used norepinephrine (Levophed) and epinephrine (Adrenalin). All the monkeys tested with these drugs at 750 gram-cm of trauma force were paraplegic (Fig. 10). It was not possible to maintain the blood pressure at normal or slightly elevated readings using these agents.
Discussion

The principle of vertebral immobilization following trauma to the spinal column has been an undisputed dictum closely observed for many years. Hippocrates stressed the importance of vertebral alignment and advocated the use of simple pressure over the point of deformity for reduction of the fracture. The introduction of traction as a method of reduction is difficult to date, although reports of primitive attempts at such a procedure are found among the writings of Hippocrates' time. Ambrose Paré (1564) developed a wooden frame on which the patient was placed, traction being exerted by two assistants, the vertebral displacement being reduced by manual pressure. In the 19th century, Wilkens used carbonized silver wire to make a figure of eight ligature about the pedicles for fixation of vertebral dislocation after various mechanical methods of reduction. A new era for management of cervical injuries was introduced by Burrell's suggestion of using a plastic jacket following mechanical relocation and Gatesfield's use of cranial tongs.

The obvious purpose of vertebral immobilization is that of preventing movement of an unstable vertebral column with consequent damage to the enclosed spinal cord. All current text books and articles stress the importance of vertebral immobilization in the treatment of spinal cord injuries, but the extent to which this most basic principle is operative has not been defined. Just how rigid the vertebral column must be and to what extent even slight movement around an injured spinal cord may be detrimental, has not been demonstrated.

It is apparent from our series of experiments that rigid immobilization of the vertebrae surrounding a contused spinal cord alters the clinical course of the animal. Whereas, a 500 gram-cm injury will consistently produce paraplegia in the nonimmobilized animal, injuries of 750 to 800 gram-cm are required when the spines and spinal cord are immobilized (Fig. 3). The mechanism by which such an alteration occurs is unknown, but the figure-of-eight structure does prevent hyperflexion of the vertebra. Prevention of spinal column movement may prevent further stretch injury and disruption of the longitudinal tracts.

In the investigation of pharmacologic agents for possible therapeutic use in spinal cord trauma, immobilized animals can serve as controls for a previously unrecognized cause of variability in results. Furthermore, drugs may or may not then be shown to provide a benefit above and beyond that achieved by an almost universally applied surgical principle (i.e., immobilization of the spine). None of the agents used in our second experiment appeared to be of clinical benefit under our experimental conditions. The rational application of drug treatment in spinal cord injury presupposes an adequate description of the sequential biochemical alterations in tissue following impact injury. At one time, central hemorrhagic necrosis was thought to be the result of vasospasm attending the release of catecholamines specifically norepinephrine, from nerve terminals in the central gray matter. One to two hours following cord injury, some investigators have found marked elevations of norepinephrine levels in the central gray; pretreatment with alphamethyltyrosine, reduced these levels and moderated the severity of developing hemorrhagic necrosis. Several studies have failed to confirm an increase in catecholamine content following trauma. In the present experiment, phenoxybenzamine, an alpha-adrenergic blocker, and methyldopa, which is thought to decrease central sympathetic flow, did not appear to alter the course of pathophysiologic events.

Whatever role biochemical alterations play in the development of the spinal cord lesions, the final mechanism involves disturbance of blood flow in the spinal cord and changes in vascularity. Immediate decreases in blood flow in the spinal cord are seen in both the central gray and white matter, although they may
take two to three hours to develop fully. Some studies have demonstrated a subsequent hyperemia in the white matter, although the white matter itself may become necrotic during the next few days. During this period, flow in the central spinal cord completely ceases in necrotic areas. It was hoped that the systemic use of either a plasma volume expander (Dextran) or of catecholamines (norepinephrine, ephedrine), would improve perfusion of the spinal cord through general effects on the cardiac output and arterial pressure. No beneficial effect was observed and it was not possible, in the present study, to evenly maintain arterial pressures at reproducible levels.

Cellular elements in the necrotic center of the lesion in the spinal cord are eventually destroyed. Presumably, a border zone exists in which some tissue might recover if the effects of chemical and blood flow disturbances were blunted. Recent work has shown that phenobarbital can exert a protective effect on cerebral tissues rendered ischemic. Unfortunately, no similar benefit was demonstrated in our experiment. It is possible that both the tempo with which spinal cord injury progresses and the inability of intravenous agents to reach damaged tissue differ greatly from conditions obtaining in cerebral vascular occlusion. Steroids, especially hydrocortisone, have been previously shown to improve results following experimental spinal cord injury. These drugs are known to have a significant influence on vascular support by maintaining vascular integrity. It is also thought that they act at the cellular level by stabilizing lysosomal membranes and thus preventing autolysis. A clinical benefit in human spinal cord injury has yet to be demonstrated.

In summary, the present study confirms and quantitates the utility of mechanical immobilization in spinal cord injury. When this therapeutic approach is strictly applied in an experimental model, further benefit from the use of a wide variety of pharmacologic agents cannot be detected. The selection of such agents is hampered by our incomplete understanding of the pathophysiological events which follow spinal cord trauma.

References

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