REVIEW ARTICLE

Acute spinal cord injury: a review of recent studies of treatment and pathophysiology

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The number of Canadians who sustain major injuries to the spinal cord has increased sharply over the past several decades, mainly because of high speed travel.[1] Although our ability to treat certain aspects of spinal cord injuries has improved, there is a group of patients for whom there is still no effective treatment. These patients sustain a major cord injury with immediate and total loss of neurological function below the level of the injury and show no signs of improvement during the first 24 hours. In virtually every such case the neurological deficit is permanent and completely refractory to treatment. It is towards this group that a great deal of research has recently been directed. In 1968 the gloomy prospect for the patient with a major spinal cord injury was brightened by a report that paraplegia may be prevented in experimental animals by the early application of local hypothermia to the injured spinal cord. Monkeys injured by dropping a weight on to the spinal cord were treated with hypothermia and recovered with little or no neurological deficit, while all of the control animals were completely paraplegic.[2] Although it is still not proven that local hypothermia is of value for human spinal cord injuries, much of the recent research suggests that the traumatized cord suffers not only from the physical injury at the time of trauma, but that after the injury a vicious circle of pathological changes may set in which causes further damage to the cord. It may be possible to counteract this auto-destructive, secondary chain of events by means such as hypothermia. The purpose of this paper is to review recent developments in this field, and to discuss their clinical value.

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Local hypothermia

Albin, White and colleagues found no harmful effects in animals from lowering the temperature of the normal cord to 10°C. by circulating cold saline at 4 to 6°C. at 100 ml. per minute over it.[3, 4] They then studied the value of local hypothermia applied immediately after injury to the spinal cord of dogs. The animals were injured by dropping a 20 g. weight 20 cm. (400 gram-centimetre force or 400 gcf) on to the exposed cord in the low thoracic region.[5] This method of experimental cord injury had been developed many years before by Allen[6] and had also been used by others.[7, 8] The cords were cooled for 2.5 hours and the return of neurological function was much better than in the injured control animals.[5] Albin and White then observed the effect of delayed cooling on the traumatized cord. This was the important experiment which elicited great clinical interest, because if cooling was to be useful for patients it had to be effective even after a delay of several hours, to allow time to bring the patient to hospital and set up treatment. They used monkeys to make the experiments as relevant to the clinical situation as possible. The results were very encouraging. They found that of 13 untreated monkeys injured by dropping a 20 g. weight 15 cm. (a 300 gcf) 12 remained completely paraplegic and one recovered a flicker of movement.[2] In contrast, of 14 similarly injured monkeys treated by local perfusion of the exposed cord with normal saline at 2 to 5°C. for three hours beginning four hours after the injury, 13 recovered completely and one almost completely.

Many investigators, including the present author, were stimulated by this report to experiment in spinal cord trauma. Unfortunately, subsequent investigations have dampened the enthusiasm for hypothermia because the results have not been as dramatic as those reported by Albin's group, and there has been criticism of the weight-dropping technique. Ducker and Hamit[9] found that some untreated dogs injured by a 375 gcf regained some voluntary movements while the group whose cords were cooled, although statistically superior in recovery to the untreated group, did not recover completely. In addition, cord cooling was not more effective than treatment with dexamethasone. Dexamethasone and other glucocorticoids have been used clinically in spinal cord trauma for several years without definite evidence of major benefit. Kelly *et al.*,[10] studying the effects of hypothermia on dogs injured by a 400 gcf, also showed variability of results in the hypothermic and nonhypothermic groups. In nonhypothermic dogs, two out of 14 recovered full function, while in dogs given hypothermia immediately after injury three out of 10 recovered completely and in those given hypothermia four hours after injury five out of 14 recovered completely. The figures for those remaining completely paraplegic are five of 14 for the nonhypothermic group, two of 10 for the immediate hypothermic group and one of 14 for the delayed hypothermic group. Campbell and colleagues[11, 12] studied the effects of a 400 gcf on cats and found that two of 17 nonhypothermic cats became ambulatory while five of 11 cats treated with hypothermia immediately after the injury became ambulatory.

Although these studies provide evidence that hypothermia is of some therapeutic value in this type of cord trauma, it was not found as consistently beneficial as had been reported by Albin's group. These studies also indicate that the weight-dropping model did not produce a consistent injury as the recovery of untreated, cord-injured animals showed. Also, from the four reports of local hypothermia with the weight-dropping technique Ducker and Hamit were the only authors to select at random the treated and untreated

groups and to make post-operative evaluation without knowledge of the treatment rendered.

Further evidence that the weight-dropping technique does not injure the cord in a constant, reproducible manner comes from the work of Donaghy and Numoto[13] who used a strain gauge to measure the force exerted on the spinal cord of dogs by a 20 g. weight dropped 30 cm. (600 gcf). The force in 10 animals ranged from 0.9 to 4.9 pounds with a mean of 3.2. Tomasula *et al.*[11] found that lesions in their animals varied considerably after traumatization at 400 gcf and concluded that the weight-dropping technique "cannot be relied upon for consistent production of a standardized lesion in a large series of animals".

Other methods have been developed for producing consistent and predictable degrees of experimental spinal cord trauma. Tarlov[14] inserted different sizes of balloons into the extradural space and inflated them at various rates. The balloons were placed anterior to the cord. Although he was mainly concerned with the compression effects of neoplasms on the spinal cord he did attempt to simulate with this model the compression of the cord in acute injury. The present author has used an inflatable silastic cuff which is also inserted extradurally but in contrast to Tarlov's balloon, the cuff completely surrounds the cord.[15] Rapid inflation of the cuff produces circumferential compression of the cord comparable to that occurring in clinical fracture-dislocation of the spine, which is the commonest mechanism of cord trauma in man. Richardson and Nakamura[16] have produced a modification of the weight-dropping technique which they believe is more reliable. A rod is dropped on the cord and left to compress it for a period.

In contrast to the many experimental reports on hypothermia for spinal cord trauma, there have been only two clinical studies reported. One describes only the technique for producing local hypothermia of the spinal cord[17] and the other describes one patient with an acute cord injury treated with hypothermia but without benefit.[18] The present author has used local hypothermia in four patients with major spinal cord injuries. In each there was total loss of motor and sensory function below the level of the lesion, and the patients arrived in our unit within a few hours after their injuries. Two patients showed no changes in neurological function below the injury level, and two showed some return of function. One of these recovered sensation over the trunk and legs after a bursting type of compression fracture of C_5 and the other partially recovered motor and sensory function in his legs after a T12-L1 fracture-dislocation. The recovery in the patient with the cervical injury is more significant, the recovery in the patient with the thoraco-lumbar dislocation being probably mainly due to root recovery. However, in the latter patient there may also have been partial cord recovery because he regained some perianal sensation and the sacral segments of his cord would likely have been below the T12-L1 vertebral level.

The rationale for the use of hypothermia in spinal cord injury derives from the previously demonstrated prophylactic and therapeutic effects of hypothermia on the brain.[5] Temperature reduction will markedly decrease metabolic activity and therefore increase the tolerance to ischemia and hypoxia.[19-21] As well, hypothermia is said to reduce edema and inflammation.[22, 23] Albin *et al.*[2] postulated that spinal cord trauma produces "intrinsic damage to the vascular supply of the affected area" such as "vasospasm" and that hypothermia produces its beneficial effect by counteracting these vascular changes and their resultant ischemia, hypoxia and edema. The longest delay between injury and treatment which has been used experimentally is four hours and it is not known if any benefit would still result after a greater interval. It would seem that if this form of treatment is to help it must be performed as soon as possible after injury. There has been insufficient experience with the experimental and clinical use of hypothermia for spinal cord injury to allow firm conclusions to be drawn. Further experimental studies must be done and more clinical experience gained with the technique before hypothermia can be accepted as a proven treatment for spinal cord injury.

Steroids

Glucocorticosteroids have been very effective in the treatment of cerebral edema including that accompanying cerebral trauma. Steroids have also been used in patients with spinal cord injuries, but there is no definite evidence that they have improved the ability of the traumatized cord to recover. However, there is some experimental data that indicate their value. As mentioned above, Ducker and Hamit[9] studied the effectiveness of steroids in dogs injured by a 375 gcf. One group of animals was given intramuscular steroids consisting of dexamethasone for two days, commencing at three hours after injury, followed by methylprednisolone for seven days; the other group was given a single intrathecal dose of methylprednisolone at the site of trauma three hours after injury. The dura was not opened in these animals. Both groups recovered to a significantly greater extent than the untreated control group in which the dura was opened at three hours after injury and in which no other treatment was given. Richardson and Nakamura[16] studied the pathology of the spinal cord of cats injured by the rod impact technique and found that methylprednisolone given intraperitoneally immediately after injury, and up to 48 hours thereafter, produced a marked reduction in the pathological changes. Electron microscopy showed that in the steroid-treated animals the basement membrane was thinner and the endothelial cells were less swollen than in the controls.

Diuretics

The use of diuretics for reducing cerebral edema which follows head injury is of established clinical value. Although diuretics have also been used clinically in cases of spinal cord injury[24, 25] their value is uncertain. Experimental evidence suggests that they may be of value. For example, Joyner and Freeman[8] administered urea intravenously to dogs immediately after injury by the weight dropping technique (375 gcf) and found that all 10 treated animals but only four out of nine control animals returned to normal. They observed less cavitation in the cords of treated animals. Richardson and Nakamura[16] studied the effect of mannitol in electron-microscopic studies of impact injury in cats and found that it reduced the swelling of the endothelial cells and also of the astrocytic processes.

Hyperbaric oxygen

Studies have been made of the oxygen supply to the injured spinal

cord and of the effect of hyperbaric oxygen (HBO). Kelly *et al.*[10] estimated spinal cord oxygen tension (Po_2) before and after lesions inflicted at 400 gcf in dogs, and found a reduction in the Po_2 of the injured segment after injury, using both surface and needle oxygen electrodes. The reduction was seen within a few minutes after injury and continued for several hours. Hypothermia started 2.5 hours after injury and continued for three hours did not improve spinal cord Po_2. Maeda[26] injured the dog spinal cord by forceps compression and then recorded the Po_2 of the normal and injured cord by means of an open-tipped oxygen electrode. After injury the Po_2 fell during the three-hour observation period. Treatment in HBO chamber at up to three atmospheres pressure beginning 3 to 72 hours after injury, produced improvement in the Po_2 of the injured cord. No studies were done by Maeda on functional recovery after HBO. Hartzog, Risher and Snow[27] studied the therapeutic value of HBO at three atmospheres on baboons traumatized by the weight-dropping technique at 334 gcf. Only one of five animals not treated with HBO regained motor function while all of five animals given three 45-minute exposures at 3, 11 and 21 hours after trauma were able to walk. No clinical studies have been reported on the use of HBO in patients with cord injuries.

Monoamine synthesis blockade

One of the newest approaches to the therapy of spinal cord injury was recently presented by Osterholm and Mathews[28] to the Joint Meeting of the International Medical Society of Paraplegia and the 18th Spinal Cord Injury Conference of the United States Veterans Administration in Boston in October, 1971. They found that the norepinephrine concentration rose markedly in the injured spinal cord in animals subjected to a 500 gcf. They then found that alphamethyltyrosine given 15 minutes after the injury to block the synthesis of norepinephrine resulted in improved neurological function as compared with that of the control animals. It was their hypothesis that norepinephrine released at the site of injury causes severe vasoconstriction which leads to ischemia and hemorrhagic necrosis of the cord. This approach may give a useful clinical lead even though, unfortunately, alphamethyltyrosine in the doses used was nephrotoxic. Studies with other blocking agents such as dibenzylene are under way.

Myelotomy

Approximately 60 years ago A. R. Allen of the University of Pennysylvania introduced the weight-dropping technique which has become the most frequently used model of experimental spinal cord injury.[6] He was a neurologist and neuropathologist and he became impressed by the extensive hemorrhages which occurred in the cord, especially in the grey matter, within the first few hours of injury. He concluded that the "question of impact to the spinal cord had two main factors: (1) the direct injury to the axis cylinders from the impact and (2) the outpouring of serum and blood into the substance of the cord".[29] He felt that this latter factor was injurious to the cord because the traumatic hematomyelia could exert pressure on the remaining cord substance and also because this exudate "would in time, through chemical change, give rise to a biochemical irritation with destruction of tissue." To prevent these events he let the blood escape from the cord by making a median longitudinal incision into the cord at the site of injury. He used dogs and subjected them to a 450 gcf; those with myelotomy improved.[6]

He also described three patients in whom he performed myelotomy and concluded that it was beneficial.[29] Freeman and Wright[7] also studied the effects of myelotomy performed immediately after trauma in rats and dogs injured by the weight-dropping technique and found that neurological recovery was better in those treated by myelotomy. They postulated that hemorrhage into the cord produced edema and inflammatory reactions and that this resulted in pressure on the remaining cord substance. As the pressure increased capillary circulation would cease and anoxia ensue. "Thus, permanent damage could result from the sequelae of injury rather than from the direct effects of injury itself." Recently, Benes[30] reported in his monograph on spinal cord injury that he has performed myelotomy in 20 patients with cord injuries. Although he was unable to reach definite conclusions about its value, he noted that four patients improved to the point where they were able to walk with assistance.

Spinal cord regeneration

Work has continued in the past few years on spinal cord regeneration. Many new approaches have been tried but nothing of practical clinical value has resulted. Freeman's group directed attention to the fibrous scarring which develops in the injured segment forming a major obstacle to regeneration of the axonal pathways. They experimented with several agents to prevent this, including subarachnoid administration of trypsin,[31] desoxyribonuclease and fibrinolysin[32] and irradiation of the injured segment,[33] all of which reduced scarring but failed to produce regeneration and functional recovery. Other attempts by Freeman's group to reduce scar formation and promote regeneration have included anastomoses of peripheral nerves to the proximal or distal severed cord segment, spinal cord suture[34-37] and transplantation of cultured central nervous system tissue into the gap between the ends of the severed cord.[38] Freeman also removed portions of the vertebral column to allow the severed ends of the cord to be brought together.[37] Campbell's group has also been very active in this field and they have attempted to join the severed ends of the cord by a Millipore bridge.[39, 40] Others have sought to stimulate regeneration by systemic injection of various nerve growth factors[41] including homogenates of central nervous system tissues.[42] One recent electron microscopic study clearly showed that axons are able to regenerate in the proximal end of the hemisected spinal cord but the regenerated axons do not grow across the gap.[43] Regeneration in the central nervous system was the subject of a recent symposium[44] and perhaps it is not too optimistic to hope that with this sustained interest, clinically useful applications will emerge.

Recent studies of the pathophysiology of spinal cord trauma

Several studies have been done on the pathophysiology of experimental cord injury produced by the weight-dropping and other techniques which show that following injury vascular and biochemical changes lead to complete infarction and necrosis of the injured segment. Ducker and Assenmacher,[45, 46] using histological as well as microscopic photographic techniques, observed the microcirculatory changes on the dorsal surface of the cord traumatized at 300

to 500 gcf. In the more severe injuries there was vasomotor paralysis with intravascular stasis in the capillaries and venules. Vessel walls showed an inflammatory response with diapedesis, and cord edema was seen. The "damming up of the entire circulatory system" of the injured segment resulted in hemorrhagic necrosis and formation of intramedullary hematomas. Several investigators[10, 11, 47-50] have studied sequential sections of cord traumatized by the weight-dropping technique and have contrasted the effects on white and grey matter. As early as two minutes after injury, the grey matter contained petechial hemorrhages which gradually increased and coalesced so that by three to four hours hemorrhagic necrosis of the grey matter had occurred. Changes in the white matter evolved more slowly and consisted of swelling and disintegration of myelin sheaths and swelling of axis cylinders. It was concluded that these changes were due to the "direct effect of the traumatizing force and to the impairment of the blood supply to the injured area".[49] Dohrmann, Wagner and Bucy[51] made electron microscopic studies of the blood vessels of the monkey spinal cord after a 300 gcf. Fifteen minutes after injury they observed ruptures of the walls of muscular venules in the central grey matter. Collapsed capillaries were seen at one hour. By four hours they saw severe vacuolation and swelling in the endothelial cells of capillaries in the grey and white matter, changes they believed due to ischemia and stasis. Kamiya[52] used a microangiographic technique to study the circulation of the cervical cord of dogs following anterior spinal cord compression by various compressing agents and found the major circulatory insufficiency in the central arteries branching off from the anterior spinal artery rather than in the anterior spinal artery itself. These central arteries were kinked and compressed.

Spinal cord blood flow studies have been made using a variety of techniques including the Peltier thermoelectric device,[53] the heat clearance probe[54] and the radioactive xenon washout method,[55] but only recently have they been applied to the study of cord trauma. Palleske, Kivelitz and Loew[56] compressed the spinal cord of pigs by an epidural balloon which was placed alongside the cord and inflated for 30 to 90 seconds. They found that at the stronger degrees of compression, "the local result was to stop the circulation" in the cord. Their experiments lasted for only a few minutes after the compression ended. They found that after release of the compressing force, the blood flow quickly returned and even exceeded normal levels for two to four minutes. Ducker[55] studied the cord circulation for longer periods after compression and noted in dogs injured by the weight-dropping technique, a progressive fall in cord blood flow at the injury site which lasted for hours. Further evidence that blood flow is reduced at the site of injury comes from the studies of the partial pressure of oxygen (Po_2) in the injured segment; the studies mentioned above employing oxygen electrodes and polarography have shown a marked reduction in the cord Po_2 after injury.[10, 26, 55] Locke *et al.*[57] measured lactic acid in the cord of monkeys subjected to a 300 gcf and found it elevated for 12 hours following injury. They regarded this as evidence that the injured cord becomes ischemic and that "ischemia, with resultant decreased oxygenation and perfusion, plays a significant role in the pathological processes involved in spinal cord injury."

The actual mechanism for the reduction of spinal cord blood flow after trauma is not known. It may be a direct, mechanical effect on blood vessels or there may be a biochemical explanation. For example, as mentioned above, Osterholm and Mathews[28] have suggested that the increased amounts of norepinephrine which accumulate in the traumatized cord after injury cause vasoconstriction of the blood vessels of the cord with resultant ischemia and necrosis.

Thus there is much evidence to suggest that trauma causes a reduction in the blood flow in the injured cord. This concept provides the rationale for treatment with hypothermia or hyperbaric oxygen; the former reduces the cord's demand for oxygen while the blood flow is compromised, and the latter enables the demand to be met.

It should be noted that not all investigators believe that vascular changes in traumatized cord cause further damage to the cord. Tarlov[14] and Gelfan and Tarlov[58] performed numerous experiments on spinal cord injury although they were mainly concerned with studying the effects of chronic compression of the cord such as that accompanying spinal cord tumours. It was their conclusion that the direct mechanical effect of compression was more important than ischemia or hypoxia due to vascular obstruction. Fairholm and Turnbull,[59, 60] using microangiography to study the microvasculature of the injured spinal cord, also supported the direct, mechanical theory. Rabbits were subjected to injuries at 50 to 300 gcf and dogs at 300 gcf; half the animals were able to sit at two days, indicating partial recovery, while the others remained completely paraplegic or almost so during the observation period which lasted up to 14 days after injury. Although there was a marked reduction of blood flow in the central zone of the cord, the blood flow in the peripheral zones, consisting mainly of white matter, was fairly well maintained. Their interpretation of the histological sections was that tissue changes were characteristic of mechanical destruction. They concluded that the "microvasculature is relatively resistant to trauma" and that the principal cause of damage was the direct mechanical injury. Whether the same findings would have been present with higher degrees of compression which rendered all the animals permanently paraplegic is not known.

There have been several recent studies of impulse conduction in the injured spinal cord which are important for several reasons. Transmissions of afferent and efferent impulses across the injured segment may assist in determining the reliability of the methods of experimental cord injury[12] and may serve as a guide for judging the effectiveness of treatment. In clinical practice such transmission may also be used to indicate the severity of the injury and the effectiveness of therapy. Donaghy and Numoto[13, 61] studied the prognostic value of cortical evoked response in dogs and in patients with spinal cord injuries and found that the early return of sensory evoked potentials was a favourable prognostic sign for return of spinal cord function. It is hoped that further refinement of these neurophysiological techniques may help to select patients for treatment and to assess the results.

Conclusions

Much work has recently been done on the therapy and pathophysiology of spinal cord trauma. There is evidence that the spinal cord suffers not only from the direct injury to axons and blood vessels at the time of injury but also from a secondary chain of events which results in ischemia, hypoxia, edema and ultimate infarction of the cord. If this is true, then it may be possible to counteract this autodestructive process by local hypothermia, steroids, diuretics, hyperbaric oxygen or monoamine synthesis blockade. It is clear that if these efforts are to be beneficial they must be applied as soon as possible after injury and before infarction has occurred. Our own criteria for using local hypothermia include its application within a few hours after injury, preferably within four hours. Unfortunately, there is as yet no effective means of promoting regeneration after the cord has become infarcted, although the vigorous research now being done in several centres offers some hope that this may be possible in the future.

Résumé

Les lésions aiguës de la moelle épinière: les données récentes sur leur physiopathologie

De nombreux travaux ont été récemment consacrés à la physiopathologie et au traitement des traumatismes de la corde spinale. S'il est incontestable que le traumatisme lèse directement les cylindraxes et les vaisseaux, il existe également des preuves que la moelle subit des lésions secondaires se traduisant par de l'ischémie, de l'hypoxie, de l'oedème et, finalement, par un infarctus de la cord spinale. Si cette hypothèse devait se vérifier, il serait alors possible de combattre ce processus d'autodestruction par une hypothermie locale, l'administration de stéroïdes, de diurétiques, d'oxygène hyperbare ou par blocage de la synthèse de la monoamine-oxydase. Il est clair que, pour avoir un effet favorable, ces mesures doivent être prises dans le plus bref délai après la lésion et, évidemment, avant l'apparition de l'infarctus. D'après notre expérience, l'hyopthermie locale doit être instaurée dans les quelques heures consécutives à la lésion et, de préférence, dans un délai maximum de quatre heures. Nous ne disposons pas encore de moyens efficaces de favoriser la régénération de la moelle épinière après que celle-ci a subi l'infarctus. Les vastes recherches qui sont en cours dans plusieurs centres permettent cependant d'espérer réaliser cette régénération médullaire à l'avenir.

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