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Spinal Cord Injury and Tools in Research for Future Therapy

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Abstract

While serving with the 91st evacuation hospital as a combat surgeon in Viet-Nam (1966-67), I treated several soldiers suffering with spinal cord injuries. These injuries occurred when the soldiers were taken to an area by helicopter and literally dropped off in the combat zone. The helicopter pilots transporting them to the combat zones with vegetation obscuring their view misjudged the distance to the ground. The soldiers jumped from a greater height and were injured as they fell to the ground. So instead of jumping out of the helicopter for just a few feet, the soldiers would leap, find they had a much greater jump, and would fracture their spine and injure their spinal cords. These soldiers would be brought to our hospital by helicopter and were found to have sustained a significant vertebral column fracture dislocation with an accompanying spinal cord contusion or compression. And thus would begin the long, long road for treatment of the spinal cord injury and frequently they were found to have a fracture dislocation at T12-L1 with paraplegia.

Keywords: Spinal cord injury; Research on spinal injury treatment

Introduction

The clinical practice guidelines for the treatment of spinal cord injuries have been determined from two professional groups; namely, the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (AANS/CNS) [1,2], who deals mainly with acute care treatment. The Consortium for Spinal Cord Medicine has written guidelines for both the acute and chronic care of these patients [3]. More weight is given to randomized, prospective, controlled clinical trials than to clinical cases describing one or more patients, who responded to a particular form of treatment.

The acute care for a patient with a spinal cord injury begins at the scene of the accident with immobilization of the patient's spine as the patient is transported to a trauma center. In addition, life-threatening issues have to be addressed immediately such as severe blood loss, an obstructed respiratory pathway, other major organ injuries, and shock. As a result of the improvement in the early phase at the accident scene, the number of complete spinal cord injuries has dropped from 55% to 39% at most regional trauma centers [1,2]. Besides this immobilization, few therapies for the treatment of spinal cord injuries have proven to be effective. Immobilization reduces the motion of the spinal column. Despite this progress, however there has not been any pharmacological therapy rendered at the scene of the accident which has been universally effective. There have been some anecdotal suggestions that intravenous administration of ice cold saline preserves spinal cord function, but this has not stood the test of time.

Decompression of the spinal cord has been the mainstay of therapy for spinal cord injuries. It is thought that it is helpful to take the pressure off of the spinal cord and to remove any compression coming from bone fragments, ruptured disc material, hemorrhage, and fluid. After surgery the patient is placed in traction in an attempt to realign the vertebral column. But even this therapy is not free from controversy as there are some who question the utility of this treatment and the timing of the surgery. Although there is some evidence in animal studies that decompression is helpful [4], this information has not been translated into therapy for humans with certainty. No prospective clinical trials of the benefits of decompression have been conducted for humans and the timing issue has not been resolved. One study of a large case series suggests that it is better to perform the decompression surgery within six hours of the spinal cord injury [5]. There are some who maintain that surgical decompression may be harmful [6]. Two professional groups have taken the position that decompressive surgery is not the standard of care but is an option [7].

Several human clinical trials of neuro protective therapy have been completed and as of now,

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no medication at the time of the spinal injury provides any more protection or therapeutic effect. The two medications most frequently employed and discussed are Methylprednisolone and ganglioside GM-1. Two separate panels have reviewed the various studies and trials and have concluded that the administration of these medications does not constitute the standard of care, but are options.

Three separate trials were carried out by the National Acute Spinal Cord Injury Study (NASCIS) in 1984, 1990 and 1997 [8]. These studies were launched because it was thought that Methylprednisolone inhibited ischemia in animals and prevented axon degeneration and inflammation. The accumulated information which suggested improvement in the status of the patients with this therapy was very weak and not conclusive of any therapeutic benefit. In fact, some of the patients developed serious infections, gastro-intestinal hemorrhages, and respiratory complications.

Also, the finding of the studies for the ganglioside GM-1 were not encouraging as this medication did not prevent the cellular death or apoptosis nor did it induce neuronal sprouting in the animals [1,2].

Various Tools for Research for Future Therapy

Approximately 18 years ago on July 4, I received a telephone call from a colleague who was an obstetrician-gynecologist. He reported that his son dove into shallow water while swimming with his friends that weekend. His son, who was a pre-medical student, had just completed his junior year at college soon planning to apply for medical school. At that moment he had been admitted to strong memorial hospital in Rochester, NY (New York). The x-rays showed an unstable C4 fracture dislocation and his son had a C4-C5 spinal cord involvement and sensory level. He had no movement in his arms or his legs but some movement of his shoulders. He was breathing on his own but with some difficulty. The doctors had placed him in a Halo apparatus to stabilize the fracture and surgery was scheduled to decompress the spinal cord and to stabilize the cervical vertebrate. I tried to be as truthful as I could be without taking away his hope of recovery, but I did tell him that the prognosis for functional recovery was not very good, in fact, awful. I encouraged my friend to consider sending his son to Craig rehabilitation in Denver as soon as he was stable and in a condition suitable for traveling. A decompressive surgical procedure and stabilization were done in Rochester. Post-operatively, his son required a tracheotomy and was put on a respirator in order to breathe. His sensory level now was at C3. Unfortunately, the young man continued to deteriorate with cardiac arrests, respiratory problems, pulmonary emboli, and fever. In addition, he could not eat and probably would never be able to eat or swallow, breathe independent of a respirator, nor move his extremities. As the weeks went by, his condition deteriorated and the patient communicated with his parents that he knew he was not going to make it nor was he ever going to have a satisfactory recovery. After discussing this situation with his parents and with his doctors, a decision was made jointly to turn off the respirator and allow him to die. In this case death was felt to be the best choice. Indeed it was very, very difficult for the parents to acquiesce in this decision to allow their son to die.

Over the past 20 years, there has been a great deal of progress in the development of research tools in the field of spinal cord injuries. Studies with animal models have been thwarted to some degree by the various animal rights groups, but these experiments have been very important to the research of spinal cord injuries. Advances in cell culture techniques and imaging techniques have contributed to the understanding of genetic mechanisms. These tools have aided our knowledge about the molecular and structural levels.

Molecular biology-based techniques such as DNA or protein analysis have contributed to the study of growing neurons in isolation or with gill cells such as oligodendrocytes or Schwann cells. These approaches contribute further in the study of axonal growth and myelination.

Numerous molecules that regulate the growth of the axon have been studied in the fruit fly [9]. Multiple transgenic animals have been examined in order to learn about the genetic and molecular basis by which spinal circuits, neuronal subtypes, and synapses are formed [10]. Animal experiments are essential in obtaining information about the spinal cord and injuries that affect it. There is no ethical way that science can get the information needed to treat human patients without doing initial research on animals. For example, we learned from rodents that the neurons in the spinal cord can regenerate after an injury [11]. In 2000, the International Spinal Research Trust published guidelines for an animal model to be used for the study of spinal cord injuries [12].

1. The nature and the extent of the lesion must be defined.

2. A histological method has to be employed to detect axonal growth through the lesion.

3. There has to be a method employed to analyze the functional synaptic transmission beyond the lesion.

4. There has to be a behavioral measure to detect the restoration of circuits.

Various animal models have been developed that reproduce compression, contusion, and transaction [13].

The research on spinal cord injuries has to be standardized as much as possible. The transaction techniques must be the same and must be complete so that everyone knows that any recovery of function is due to axonal regeneration and not to some spared spinal cord circuitry. If all of the axons are not severed, then sparing and sprouting from uninjured axons might become an issue. If the durra mater is injured, then this could become a source for fibroblasts to form scar tissue or promote repair. In addition, there are several standardized impactors that have been developed that replicate similar injuries.

There is also the issue of genetic variability. For example, humans and rats can develop a cavity in the spinal cord in response to an injury. No cavity forms when the spinal cords of mice are injured. Sometimes various strains and species of an animal population can differ which would affect the results. Metz et al. [14] has called attention to the varying lengths of spinal cords in humans and in some animals. For example, the human spinal cord is four times as long as the rat's nervous system. If a contusion affects 3 cm of a human spinal cord, which is over 10 times the length of a 2 mm area affected in a rat, and some regeneration of the nerve fibers occurs in the rat which results in some restoration of function in the rat, that is equivalent to only a fraction of the distance in a human that is required to restore function in humans. Oligodendrocyte cells can remyelinate axons in rats and humans but far more length is needed in humans compared to rats [6].

Some types of monkeys have specific antibodies that attack and

inhibit the survival of human cells. Also the metabolism of anti-rejection drugs differs in nonhuman primates and humans. At the present time, there is no standard laboratory animal with which researchers study fine motor control of the upper extremities or the loss of proprioception of the limbs.

Most of the research is aimed at developing and testing the recovery of motor function in animals. So far, there has been little or no meaningful research in areas of sexual function, bladder and bowel control, and chronic pain relief [15]. The various tools used to assess spinal cord injuries in laboratory animals include: (1) Basso, Beattie, and Brenham scale, (2) Basso Mouse Scale (BMS), (3) neuronal activity assessment by electrophysiology, (4) forepaw withdrawal, (5) directed forepaw reaching, (6) morphological assessment of recovery, (7) real time imaging of the spinal cord and (8) genetically encoded reporter molecules [16].

The Basso Beattie Brenham (BBB) scale is a locomotor test for rats based on the 5-point Talon scale. This analyses the hind leg movements of rats and assesses locomotor coordination, joint movement, foot stability, and gait stability. The Basso Mouse Scale (BMS) is a test for the recovery of hind leg locomotors function in mice. Electrophysiology is used to assess electric potentials by stimulating the cortical areas of the brain and the responses in target areas. The forepaw withdrawal is done by placing the forepaw of an animal on a heat block and measuring the time the animal withdraws that limb. The directed forepaw testing requires rats to reach under a barrier to pick up food with his forepaws. The morphological studies are accomplished using histological tissue techniques, electron microscopy studies, and antibody staining methods and all of these tests are only performed on deceased animals. The real time imaging of the spinal cord is done with MRI, CAT and PET scans which are safe tests but still are not powerful enough to detect changes in the living cells. Finally, genetically encoded reporter molecules are utilized to study axon regrowth and formation.

Some researchers have sought to find a technique that monitors the real time progression of spinal cord injuries. Biomarkers are not currently available to identify the changes in the cells of the living spinal cord, although there are a large number of potential markers, which hopefully could be used to monitor the progression of recovery from these injuries. As a result of the trauma to the spinal cord, there are a large number of biochemical reactions that are reflected in the mRNA and the protein levels. The mRNA is transcribed from the DNA and provides the transcript to synthesize new proteins. So analysis of the mRNA and the proteins provides an avenue to study the cellular changes. Microarray techniques make it possible to examine the changes at the genetic level. Already, some researchers have identified genetic variations after spinal cord injuries. Specifically, Song et al. [17,18] and Nesic et al. [19] have demonstrated that there is an increase in the interleukin-6 protein and the death of cells is regulated by the changes in the levels of the Fas protein [17-20].

Conclusion

It is hoped that study of the genetic sequences during the course of a spinal cord with injury would provide doctors with information about the molecular events that are responsible for the changes that occur. Physicians could then use this information to affect the changes during the treatment and thus avoid some of the complications of spinal cord injuries. Gene therapy approaches have been thought to be the ideal mechanism to achieve long-term local delivery of therapeutic molecules to the nervous system. Gene delivery can provide cellular support for regenerating axons [21]. Recently, research is indicating that there is a major shift in the way cancer drugs are developed and how patients with cancer are treated. Personalized therapies for patients with cancer have been discussed for years, but now researchers are using genetic information to match the drugs with the biological drivers of tumors in individuals. Personalized medicine is closer to being used as a treatment for cancer. Some facilities are able to match the genetic information about a tumor to a new pharmaceutical agent. Many of these cancer drugs are designed to target specific genetic mutations but these drugs are very expensive. By targeting the mutations, fewer patients will be needed for the clinical trials. So what has cancer to do with spinal cord injuries? Well, the more we know about using genes in medicine for cancer, the more likely we will learn more about using this information for the treatment of spinal cord injuries. Applying gene therapy has the potential in providing the injured spinal cord with some specific gene products such as proteins, which are needed for a functional recovery. Presently, gene therapy is not being used for spinal cord injuries, but it has possibilities and is being considered by researchers. The idea is to transfer a gene encoding a therapeutic protein into the injured spinal cord, which could be a growth factor or an axon guidance molecule. Animal studies and models can be used to bear this out. By using a gene rather than cell replacement therapy the dose or the amount of the protein can be controlled. By using gene therapy, researchers have succeeded in introducing growth factors that have led in some recovery of function in rodent models [22,23].

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