

Neuroscience approach in Stem cell therapy among patients with Spinal Cord Injury

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ABSTRACT

The first necessary step in researches to treat spinal cord injuries (SCI) is to understand complexities related to the neurophysiology and neurobiology changes of human SCI with stem cell therapy (SCT). The aim of this study is to identify these changes. The level of injuries is important in treatment and determination of this injury; whether it is complete, incomplete, or incomplete is valuable, as well. Loss of all neurological functions affected by this injury and physiological or anatomical continuity of central nervous system tracts occur across this lesion. Obviously, achieved result is that the maximum number of tracts can be maintained, and increase in the acute phase of illness. Stimulating the axonal regeneration by neutralizing inhibitory factors, adding positive tropisms, and creating a permissive environment is suitable. Better results that had been obtained are achieved by filling gaps with peripheral nerve grafts or transplanting Schwann cells, and fibroblasts that genetic engineering has been done on them. Ability of poly potential cells to differentiate and create neural tissues is remarkable. The relatively good success in obtaining the proper repair for axons has been reported. However, this issue also should be considered that human spinal cord injuries have significant differences with spinal cord injuries in laboratory animals. In order to be successful in doing this research, the changes of human SCI must also be considered and the use of stem cells in treating human SCI must be performed due to these changes.

Keywords: Neuroscience; Stem cell therapy; Spinal Cord Injury

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INTRODUCTION

1. Neurobiological Changes of spinal cord injuries (SCI)

Stem cell therapy (SCT) should be predictable in the future and with the aim of the many recent advances that are obtained in the laboratory neurobiology. Now, it is clear that central axonal regeneration is possible under special laboratory conditions and for mammals. Inhibitor molecules have been inactivated and a permissive environment is provided¹. Since stem cells can differentiate and turn to central nervous system (CNS),

laboratory facilities and the possibilities have become more widespread. Treatment for SCI, based on stem cell technology, is one of the possibilities. Since spinal cord injuries considered as a major cause of human death not much time passes and differences with the conditions under which, there was no cure for this disease are small². However, there is a great urgency and necessity for the results of recent research to be applied to patients; it is strictly recommended that human trials should not begin until the experimental methodology is completely worked out in an appropriate animal model. There is

also a fact that most physicians, who think about SCI treatment, do not recognize that loss of feeling may be equal to disabling as paralysis³. Autonomic disorders are also very important, and can lead to disability or overall disability. For example, there are so many differences between paraplegia caused due to poliomyelitis (causing the loss of sensory systems and systems autonomic) and SCI (in which all neurological functions is lost^{4,5}. The first point that must always remember is that each of SCI patients are different from the other patients with this disease so that any recommended treatment regimen for each of these patients should be allocated only to that particular patient. In spinal cord injuries, it is likely that the patient looks normal when the observation and examination is performed with the naked eye but when it is examined through a microscope, we will understand that there is a severe injury while spinal cord is almost intact. In SCI, spinal cord often appears to be contused, compressed, lacerated, disrupted, and in very rare cases it looks transected^{1,6}. Typically, edema and petechial hemorrhages are found in the white matter tracts and gray matter undergoes hemorrhagic necrosis (which is a reflection of the blood-rich products) in flexion injuries^{7,8}. SCI may be mild, moderate or severe, and may include multiple levels that have been developed on different sectors. The vertebral injury is related to the more severe or milder degrees of hemorrhage within the extradural, subdural or subarachnoid spaces. At autopsy, the bony column and spinal cord are removed together, so that it provides the possibility of injury repair and connect the bone to the soft tissue changes^{9,10}.

Mechanism that is used in SCI is to direct body compression and it can cause change based on the type of injury with some rotation distraction and distortion. Vertebral injuries are classified as flexion, extension, rotation, distraction and compressive. In each of these cases spinal cord is at risk, thus causing injury to the cord. However, in this case, it is unusual to find the detached fragments of bone that can cause deterioration of the cord lesion. Although hemorrhages in different parts of meningeal are common, hematomas rarely cause significant compression of cord. One of the features associated with vertebral injury is realignment of the vertebral column, that often occurs either spontaneously or following an accident^{11,12}. A microscopic change in spinal cord, which occurs after an injury, has been well understood. SCI morphology varies according to different stages that have been studied as an acute, subacute and chronic. Each of the 'curative' treatments, clearly, must be designed specifically for the stage that all these measures

are planned for that stage¹³⁻¹⁵.

Clinically, the neurological injuries are called to complete, incomplete or discomplete, that depends on the presence or absence of neurological functions below the injury level. At the segmental level, paralysis depends on the type of lower motor neurons (LMN) that arise from gray matter of brain's injury, or destruction of the associated nerve root or peripheral nerve trauma. However, disruption of a large number of tracts within cerebral white matter has a much higher importance in determining the SCI clinical picture. Below the lesion, paralysis depends on the type of upper motor neuron (UMN) that is associated with increasing the muscle contractions, increasing over the reflexes and sign of positive Babinski. In lesions of the cauda equina in which paralysis situation is associated with the weakening of the lower motor neurons, the exception occurs. This is because the roots of the cauda equina are able to regenerate and become peripheral nerves. This situation is very different circumstances, which has been compared with the intact cord^{16,17}.

2. Neuropathological Outcomes in SCI

In general, SCI rehabilitation outcomes are determined by the intensity of neurological disorders. Neurological disorder can have a reciprocal relationship with the pathology that has arisen from injury and this is due to the segmental nature of the spinal cord anatomy. It is very interesting that despite the strong forces are involved in creating injury to the vertebral and it has not the ability to withstand because of its fragile constancy; spinal cord is relatively resistant to the initial trauma. However, cord is much more vulnerable to secondary compression due to instability of the column sequence to injury. These issues are used for a very accurate examination in patients who are suspected of SCI. Aggravation of injury is very common and even when the patient is hospitalized, this problem occurs. In the acute phase, transient or permanent damage to axons in terms of histology has been shown, and this is performed by immunochemical activity of dense 'A Beta' protein (this protein is a component of amyloid precursor protein or APP within axons). These axons have their transport system interrupted, but rather are able to recover. Those who remain healthy, it is possible that be remyelinated with peripheral Schwann cell myelin¹⁸. It is known that other bare axons, formatting terminal bulb, have been disrupted¹⁹.

The first sign of injury is cord edema, which can cause swelling that is due to leakage of fluid from the capillaries. This occurs within minutes after the injury

and usually is associated with white matter parenchymal hemorrhage. Central gray matter necrosis is a common result of flexion and extension injuries. Solid cord injury without any visible hemorrhage or evident parenchymal disruption is unusual. Clinically, this type of injury is associated with central cord syndrome; the main lesions will generate in the white matter of the lateral columns that are adjacent to the central gray matter¹. In this acute phase, necrosis and in lower-scale occurrence of apoptosis is cause of neurons and glia death in the vicinity of the injured area. The impact of excitotoxic shock is also evident with the destruction caused by free radicals at the molecular level. Vascular changes that occur in response to this phenomenon, initiated by cytokines released from damaged tissues, which may happen in the first 12 hours and represented by the migration of polymorphonuclear leucocytes and vascular dilation. It seems that after these events, lymphocytes and macrophages soon afterward within 24 hours to 48 hours after injury, will present in this area. The number and proportion of these cells largely varies from case to case. Within 72 hours, fat-laden macrophages are greatly found in the area. These cells ingest myelin fragments and turn them to neutral fats using enzymes, thus they easily take them away from this area and eventually will destroy them. It is thought that reactive changes cause secondary damages to spinal cord parenchyma, which may at first seem quite intact^{7,9,20}.

The next phase is subacute stage, is characterized by forming cavity to remove debris that is performed by continuing activity of macrophages. Astrocytes, which appear for the first time about 5 days after injury, proliferate, and locate on glial fibers and finally will form irregular heteromorphic networks. Depending on the extent of arachnoid and dural tearing, collagenous fibrosis may be prominent inside and around of the cord lesion, so that the subarachnoid space is removed. The rate of collagenous scar formation is variable and is usually proportional to the amount of hemorrhage. Beyond the immediate injury, many changes will occur in the remaining cord tissues. Degeneration of Wallerian axons is a continuous process distal to the neuronal cell body. Over time, axons are decomposed distal to the injured area and their myelin sheaths are broken up into globules. Degeneration of axons and myelin breakdown can be seen near the end of the lesion (in the caudal), in the motor pathways, and in the rostral part of sensory tracts. Macrophages will remove debris and Astrocytes lay down fibers parallel to the lost axons and thus may lead to isomorphic gliosis. In addition, the loss of Wallerian

also occurs in patients who survived for 12 months or more. Other changes are more suitable including reflex deviations and the ‘plastic’ neurophysiological effects at the synaptic level arising from changes in the inhibitory signals, thresholds, neurotransmitter release and neuroendocrines. These ‘plastic’ changes are continuous²¹⁻²⁴.

In chronic or end stage of SCI, the lesion is typically composed of a multilocular cavity holes that pass through the vascular-glial pathways and are associated with regenerated nerve roots. Astrocytes and collagen fibers encounter with different degrees of different compounds and surround the cavities. It should be noted that multilocular cystic cavities are not related to posttraumatic syringomyelia but represent the remaining processes of the body healing. Appropriate amounts of gliosis, collagen, new blood vessels, macrophages (some of which are filled with iron), cause nerve roots regeneration. There is also the possibility that a limited amount of central axons regeneration occurred spontaneously however, demonstration of this fact (directly) in humans is impossible. Central Axons that myelinated by the Schwann cells have been found, but it may either be remyelinated (the same so that is described above), or possibly central axons are made to be regenerated by Schwann cells. In this final stage, the lesion is more or less static except when it is supposed that continuous increase in the loss of Wallerian degeneration of spinal tracts occur above or below the lesion and this can effect on the plasticity of neuronal synaptic network²⁵⁻²⁹.

Nerve roots also continue to grow randomly within the remaining parenchyma and outside of the cord. Another result is usually achieved in the long term is posttraumatic syringomyelia that will develop approximately 5% of cases. Other complications that occur in the long term are due to the aging process, such as atheroma of feeding arteries and intervertebral disc degeneration. This change and ligamentum flavum hypertrophy may cause spinal stenosis. These effects may be the reason for neurological changes in the long term^{30,31}. Injured structures in the Spinal cord model include: Long tract, including the corticospinal that may be disordered functionally or anatomically, neurons found in the level of injury, which most of them are motor neurons and vascular disorders increasing remyelination³². It has been shown that conventional treatment regimens include immunomodulatory drugs contribute to regenerate long tracts. Today most diets are leading to myelination and are critical for axons regeneration. The proliferation of

astrocytes leads to gliosis, which in all probability will inhibit the growth of axons³³⁻³⁵.

3. Neuroscience view with SCT in SCI

Neurons to corticospinal are located in motor cortex and are not the aim for stem cells restoration. In classification and control of Spinal cord injuries, SCT could potentially be the following forms: To stimulate endogenous stem cells to proliferate along the nerve pathway. These differentiated cells will migrate around the central canal across the ducts, similar to what is provided by radial glia in cortex. They fill and restore the anterior horn cells, which have been injured at the injury level, to control switches or messenger, as an example, they strengthen this process using Shh and to advance neural stem cells along the nerve lines³⁶. However, restoration of anterior horn cells at injury levels will provide only a small amount of clinical benefits, if it is proved that the endogenous cells population is inadequate, stem cells can be used to stimulate nerve cells in vivo. These cells must reach the appropriate area, this can be a location in which nerve cells are lost or can be along the way of neurons normal migration, the more appropriate target for treatment in spinal cord injury is long tracts. Impairment in these areas is the reason for loss of motor neurons, sensory and autonomic below injury level. Neurons that are involved in this case are at the root input levels in the brain or the sensory pathway. Lush glial proliferation in injury level is detrimental for the regeneration of axons. The goal of treatment is mentioned is little proliferation of glial. It has been shown that after cord injury, Oligodendrocyte processes lead to increased myelination in the tracts. It has been shown that mesenchymal stromal cells facilitate axons regeneration in animal models. However, this can occur according to emergence and development of Oligodendrocyte processes. Conventional methods of treatment using methylprednisolone or newer tests, including rho inhibitors can also act as a second mode. In cell based treatments, to protect or regenerate tracts, mononuclear cells or lymphocyte ancestors must be used to act as immunomodulators and scavengers. This can be a way for the growth of axons^{37,38}. Stem cells in vivo may have a tendency to differentiate along oligodendrocytic lines before reaching injured areas.

Today, management model in spinal cord injury is important and the aim of spinal cord management is: maintaining of damaged parts static by external devices to minimize the risk of further injury, optimizing of blood pressure and to maintain cord perfusion if there

is blood pressure falling, that is a result of vasomotor tone deficiency. It may be necessary to make use of vasopressors, reduce surgery pressure in the compressed cord, which followed by stability, in order to start treatment to terminate the secondary cascades and to facilitate axon regeneration. Neurological status of each patient may reflect neuropathology of the lesion. Whether there is nerve functions or not or only parts of them are preserved, is determined by the segmental level and also by any of the remaining nerve tracts in the white matter, which have been safe from injury³⁹.

However, there is one condition that there must be a number of remaining axonal tracts, although they are continuously across the lesion, but it is less than the amount that is able to continue maintenance their voluntary motor activity in the lower or upper parts. These activities must be done to have “sense”. Signals that are transmitted across the lesion will cause discomplete mode in the injuries that are not complete and make a good connection with anatomic findings related to the disease that is associated with preservation of white matter bridging in the lesion³². These discomplete patients provide very good field for neurologists who are doing the regenerating operation and these specialists are always trying to benefit the remaining functions and increase them^{40,41}. Neurological status of each of the patients with SCI will not be clear approximately within 3 weeks or more after the injury and after about a year, their situation can be improved to some extent. For these patients, there are basic principles, such as resolution of edema and return of function in the axons only parts of them is damaged. In addition to obvious neurological defects, the clinical picture in each of the cases will be so complicated with unwanted abnormal neural activity. All these cases are discussed above are composed of ‘spasms’ (reflex contractions), and painful feelings of non-obvious burns, and deviations in body image perception (phantom), and other disconcerting effects. It seems that this type of unwanted side effects of SCI are caused by increased stimulation by stimulants or by inhibiting the neuronal threshold along with the effects related to flexibility of CNS tissue. New connections are caused in response to afferent inputs, arising from the ends of sensory nerves in the skin and sensory organs of joints, ligaments, and muscles. Reflex contractions are also intensified by means of urinary tract infections, severe and painful wounds, and similar items, which are lead to enhance sensory inputs. In addition to these mechanisms, the aberrant neuronal connections are also caused by injuries. Known neurophysiological changes

and micro anatomical changes, which occur in neuronal networks, and happen below the lesion, following SCI that is dynamic, complex, and continuously evolving. Such communications, are mainly apply in the MVA, diving and sport events, and only partly gunshot or knife wounds in which the injury is more specific and more complete, so that initial principles of relative resistance of the spinal cord more will not have endurance and application. Knife wounds and those caused by sharpened bicycle spokes differ from MVA trauma, the cause of this difference is 'clean' transection. However, neuropathological sequences are similar to reaction or reactive cellular changes in the level of lesion, distal Wallerian degeneration, and altered neuropathological functions above and below^{3,5,6}.

CONCLUSION

The discovery of neural stem cells could light glimmer of hope for patients with neurodegenerative diseases or those who have suffered from nerve injuries. Spinal cord injuries often force the medical community and make them to do something. In this context, with hoping that these cells can be improved, some interventions are performed. The text is presented is an overview of the current state of stem cell research and the impact of this method and newer techniques in management of Spinal cord injury models³². Discovery of the potential use of stem cells in neural repair and regeneration is a noteworthy development in the neurosciences^{42,43}. Today, we hope that stem cells may reduce disability in these patients. Stem cells are also great bucks, and news related to their development is always a step ahead of neural development. The reality, however, should mitigate this enthusiasm. There are limited evidences of animal models in which stem cells improve functional results that are exposed to injury in their spinal cord, but methods in which improvement of function is achieved are still unknown. Witnesses obtained from uncontrolled human trials are not convincing.

We hope to obtain a successful treatment with SCT for these patients, also researchers received a result of modern technology for rehabilitation after SCT according neurosciences, and they are designed for different aspects of rehabilitation treatment and can increase the focus on cognitive skills including motor control. The goal is cognitive functioning promotion. Today, through innovative treatment programs, the best approach is performed by expert therapists. We suggest neuro-cognitive assessment and rehabilitation (NCAR) is a vital part of the patient's treatment plan in neurosurgery

such as SCI with SCT⁴³⁻⁴⁶. Finally, researchers need to modern technologies for improvement SCT according novel sciences such as neuroscience, neurobiology, neurophysiology, neuropathology, neuroimaging, neuroengineering, and other related sciences with nervous system. So we suggest to researches concurrent basic and clinical sciences in SCT.

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