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USE OF STEM CELLS FOR NERVE REGENERATION IN SPINAL CORD INJURIES

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ABSTRACT

Spinal Cord injury is a devastating neurological trauma/disorder caused by damage to the nerves in the spinal cord, which may result in major motor, sensory, and autonomic dysfunction, along with damage to the functioning of the other organ systems. Due to the limitation of current treatments for SCI, many streams are being persuaded for a possible solution such as neural prosthetics, and brain-computer interface devices, and one of the foremost lines of research is cell-based therapies which comprises of stem cells. A number of clinical trials on stem cell-based treatments for SCI are being conducted across the world. This paper uses the method of systematic review to summarize and review data on the topic and provide accurate fact-based summaries of the information collected. It provides an overview of three trials conducted each at different stages of secondary injury(acute, sub-acute, and chronic), two of them use bone marrow-derived stem cells, and the other used mesenchymal stem cells. All three of them have been declared successful with two out of three having significant, distinct positive results.

Keywords: Research, Stem Cells, Spinal Cord Injuries, Nerve Regeneration, Analysis.

I. INTRODUCTION

Spinal cord injury is a catastrophic nervous system disorder affecting 250,000 to 500,000 people every year, from either traumatic (90% of cases) or non-traumatic causes (WHO, 2013). A spinal cord injury is defined as damage to any part of the spinal cord or its nerves usually resulting in permanent changes in body functions, reduced strength and sensation below the site of the injury, and impact to the organ systems (Mayo Clinic, 2021).

It impacts the patient's social, emotional, physical, and economic well-being and also causes a significant burden on the patient's family and society. Patients who have suffered from a spinal cord injury have less than a 1% chance of complete recovery, and a mortality rate of 4 to 18%(WHO, 2013). The mortality risk greatly depends on the severity of the injury but it can be altered by the availability of good, timely medical care and also depends on the manner of transport from the injury site to the hospital and travel time between the two sites (WHO, 2013). The mortality rate also varies on the level of health care available, as the leading cause of death in low-income countries is secondary injuries that can be prevented (WHO, 2013). The leading cause of spinal cord injuries is due to preventable causes like motor vehicle accidents(36 - 48%), violence (5 - 29%, falls(17 - 21%), work-related accidents, and sports-related injuries. Traumatic SCI is 79.8% more common in males than females (20.2%), while the incidence of injury resulting in SCI is most in the age group between 15 and 29 years, and the lowest in the age group above 50(Ahuja et al., 2017). Due to the primary cause being preventable, many safeguards can be put in place such as improvement of roads and vehicles, increase general awareness of driving safely, window guards to prevent falls, and police to prevent use of alcohol while driving (Physiopedia, 2013).

Even with all the scientific and medical advancements present today the survival rates of SCI patients are severally low, and a solution for reducing the severity of the injury and increasing the patient's quality of life is necessary. Hence an innovative new solution, outside of normal treatments, which aims to decrease the mortality rate and improve SCI patients' quality of life is imperative. To this end, there have been various clinical and experimental studies being conducted across the world to find answers to this issue. Studies are being pursued in multiple different streams, such as neural prosthetics, brain-computer interface devices, pharmacological drugs for neuroprotection, cell transplants, natural growth-promoting substances, bioengineered growth scaffolds, electrical stimulation, robot-assisted training, and one of the foremost lines of research is cell-based therapies which comprise of stem cells (NIH, 2017).

Stem cells have dominated the field of regenerative medicine for the last three decades and are considered one

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of the most promising fields in modern medicine. With its ability to renew itself and differentiate to form multiple tissues and specialized cells, such as muscle cells, blood cells, and brain cells, its potential uses in the field of medicine are astronomical. It can provide us with a better understanding of the genetic and molecular signals that are involved in regulating cell division and can possibly give information on how diseases arise, which is essential in developing cures for them (MedlinePlus, 2020). Other applications include hemopoietic stem cell transplantation and ex vivo expansion of human epidermal and corneal stem cells (Watt & Driskell, 2010). Stem cells may become especially useful when it comes to spinal cord injuries, as the primary reason mammals have poor survival and recovery rates from spinal cord injuries is because of their inability to regrow or heal neurons, and stem cells offer a solution to this problem. However the clinical trials being conducted for the use of stem cells, vary in the manner in which they are conducted, and there is no universal agreement on the best method for transplantation timing, cell dosage, cell type, and mode of transplantation (Yamazaki, Kawabori, Seki, & Houkin, 2020).

This paper will help illustrate the impact and pathophysiology of spinal cord injuries. It will also provide information on the current treatments for SCI being pursued and a brief of the experimental trials that are being conducted. It will also give a brief overview of stem cells with regard to their anatomy, function, and classification, and provide an overview of stem cell-based therapies that are currently ongoing. Finally, it will provide a description of different case studies of a few clinical trials on stem cell-based therapies for spinal cord injuries. This paper centers on the main research question: can stem cells be used for neuroregeneration for spinal cord injuries?

II. METHODOLOGY

My archival research project on the thesis question can stem cells be used for neuroregeneration for spinal cord injuries, uses the method of systematic review to summarize and review data on the topic and provide accurate fact-based summaries of the information collected. I viewed PubMed Central between 2011 and 2022, and I used search terms like “Spinal cord injuries”, “stem cells”, “clinical trials”, and “spinal cord treatments”, ProQuest between 2015 and 2022, and Science Direct between 2011 and 2022.

III. OVERVIEW OF SPINAL CORD INJURIES

Spinal cord injuries affect a patient's life in every aspect, mentally, emotionally, and physically. Depending on the severity and placement of the damage, the injury often results in major motor, sensory, and autonomic dysfunction, along with impairment to the cardiovascular, urinary, reproductive, musculoskeletal, integumentary, and digestive systems (Anjum et al., 2020). Individuals with SCI also often have to cope with altered social roles and psychiatric conditions including reactive depression and anxiety disorders, with suicide rates of SCI patients being two to six times higher than that of the general population and only 12% go on to hold employment (Joe Bennett, Joe M Das, & Prabhu D. Emmady., 2022; Lee, Nam, Kim, & Hwang, 2019). Moreover, these injuries are associated with lower rates of school enrollment and economic participation, and it carries substantial individual and societal costs (WHO, 2013). SCI places an heavy burden on the economy, which is even heavier in developing countries. The cost of care on a patient is extremely high with the mean cost of acute care, inpatient rehabilitation, first year after injury, and ensuring years ranging between 56380 to $2,463,480. Different levels of injury, location of treatment, timeframe of care, etc. all play a role in the variation of total costs (Malekzadeh et al., 2022). In addition, individuals with SCI must often cope with an increased incidence of various future health complications, and patients with SCI are 2-5 times more likely to die prematurely (WHO, 2013). Survival rates have a strong correlation with the level of neurological level and degree of impairment (See Fig 1).

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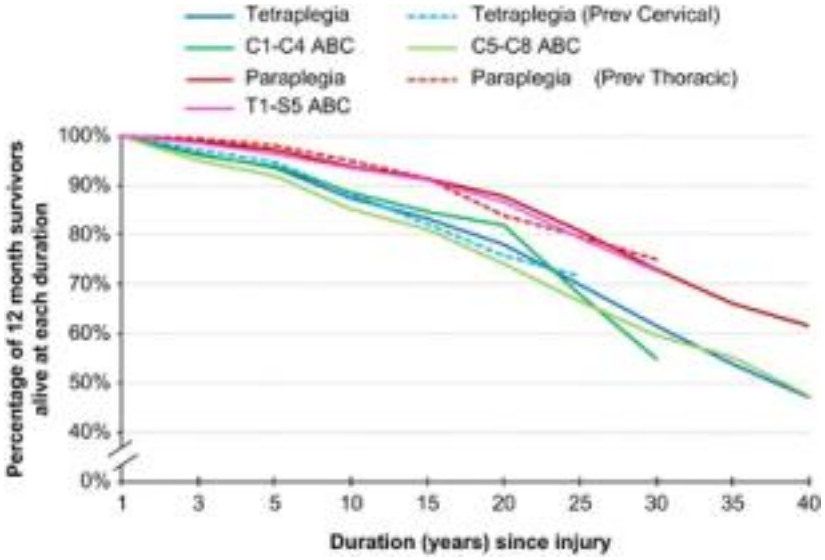

Fig 1: Shows mortality of SCI patients. Reference: (MIDDLETON et al., 2012)

Spinal cord injuries occur either by physical trauma, which includes motor vehicle accidents, community violence, recreational activities, workplace-related injuries, etc., or non-traumatic causes such as insufficient blood supply, infection, cancer, osteoarthritis, etc.(Katari Venkatesh, Ghosh, Mullick, Manivasagam, & Sen, 2019). The estimated global rate of patients suffering from SCI varies from 250,000 to 500,000 every year, with up to 90% of these cases caused due to traumatic causes (WHO, 2013). For traumatic spinal cord injuries, the in-hospital mortality varies from 4-18% and the complete recovery is less than 1% (Chhabra, Sharawat, & Vishwakarma, 2022). Therefore, prevention, early diagnosis, and superior treatment options for patients with SCI are critical for limiting complications, improving survival, increasing community participation, and improving overall health-related quality of life.

A. Pathophysiology of spinal cord injuries

Traumatic spinal cord injuries are caused by a sudden impact on the spine that fractures or dislocates the vertebrae, damaging the surrounding tissue and causing a cascade of molecular reactions in the body (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). It may result in long-term dysfunction in various organ systems and this combined with a permanent change in function, results in higher morbidity rates and a lower quality of life (Hagen, 2015). The damage as a result of these reactions is broken down into primary and secondary injury mechanisms. Primary injury is the initial stage immediately after the injury takes place and it is caused by the direct compression of the spinal cord and the bruising or tearing of its tissue (See Fig.2). Primary injury causes the destruction of neural parenchyma (a group of tissues that is essential for the functioning of CNS), disruption of the nerves and glial membrane (a thin membrane that lines the spinal cord and ventricles of the brain), and the initial impact leads to immediate hemorrhage and rapid cell death at the impact site (Anjum et al., 2020). The four major types of primary injuries' are impact plus persistent compression, impact alone with transient compression, distraction, and laceration/transection (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). The most prominent among them is impact plus persistent compression, which usually occurs when burst fractures cause bone fragments to compress the spinal cord or through fracture-dislocation injuries (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). In all cases of SCI the force of impact causes direct damage to the ascending and descending pathways in the spinal cord, disrupts the blood vessels and cell membranes, causes spinal shock, abnormally low blood pressure, vasospasm, restriction of blood flow, ionic imbalance, and neurotransmitter accumulation which can cause seizures (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). But the severity of the injury is majorly determined by the extent of initial destruction and duration of spinal cord compression. Hence, the most effective clinical treatment to limit tissue damage following primary injury is early surgical decompression of the spinal cord, which should occur within 24 hours after impact (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). The earlier the action takes place, less the extent of the primary damage which essentially defines the extent of the severity of the spinal cord injury.

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The primary injury is followed by the secondary injury mechanism that causes further tissue loss and dysfunction. Secondary injury is triggered by primary injury leading to increased chemical and mechanical damage to spinal tissues and involves multiple biochemical mechanisms that last for several weeks after trauma(Hachem, Ahuja, & Fehlings, 2017). It is caused by the swelling of the tissue from hemorrhage, inflammation, etc. and usually takes hours to develop. During this phase the area of trauma enlarges and the damage to the spinal cord leads to neuronal excitotoxicity (an action of neurotransmitters) due to increased calcium accumulation within cells and increased reactive oxygen concentrations and glutamate neurotransmitter levels and this which eventually leads to cell death (Anjum et al., 2020). This causes damage to the underlying nucleic acid, proteins, and phospholipids, resulting in neurological dysfunction (Anjum et al., 2020). A continuation of some events from the primary injury phase takes place: electrolyte imbalance which may cause coma or/ seizures, edema (swelling due to fluid accumulation), necrotic and apoptotic cell death, formation of free radicals which cause cardiovascular and inflammatory diseases, cataracts, and cancer, delayed calcium influx which results in a delay in cell growth, and immune system response or inflammation(Katari Venkatesh, Ghosh, Mullick, Manivasagam, & Sen, 2019).

Secondary injury is dived into 3 stages: acute(within a few days), sub-acute(a few days to 6 months), and chronic(>6 months). The acute secondary injury initiation is marked by vascular damage, excitotoxicity, free radical production, and increased calcium influx which leads to cell death, lipid peroxidation(when oxidants attack lipids causing destruction of lipids) which leads to membrane rupture and cell death, inflammation, edema, and necrosis (See Fig.2)(Anjum et al., 2020). If continued then the sub-acute secondary injury phase begins and is manifested by features such as neuronal apoptosis, and loss of myelin sheath which leads to the formation of scars, Wallerian degeneration (breakdown of the anterior part of the axon) results in nerve lesions which causes reduced sensations, and glial scar formation (bodies mechanism to heal itself)(See Fig.2)(Anjum et al., 2020). Scar formation in the brain or nerve tissues can result in epilepsy, seizures, or/and comma. It eventually leads to the chronic secondary injury phase of SCI which is characterized by axonal death, maturation of glial scar, altered neurocircuits, and syringomyelia (a neurological disorder that causes fluid-filled cysts to form in the spinal cord) (See Fig.2)(MayoClinic, 2022) (Anjum et al., 2020).

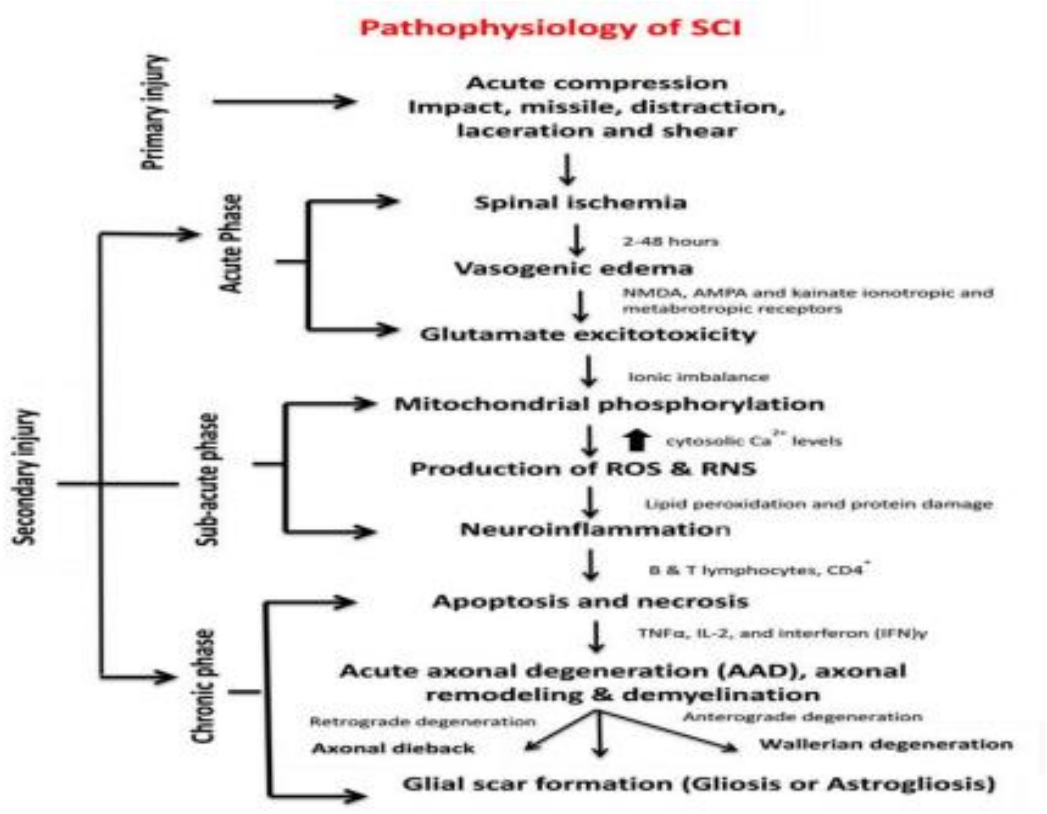

Fig 2: Diagrammatic view of the pathophysiology of the primary and secondary mechanisms.
Reference:(Anjum et al., 2020)

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Other long and short-term complications that may arise in all three stages of secondary injury are neurogenic shock due to severe hypotension and bradycardia due to a drop in blood pressure, cardiovascular complications such as orthostatic hypotension and autonomic dysreflexia (abnormal stimulation of the autonomic nervous system), effects on the pulmonary system, and respiratory difficulties which is the major cause of death, thromboembolism is common since SCI patients are at higher risk of coagulation, pressure ulcers, heterotopic ossification, bladder complications as a result of bladder and sphincter being hypotonic after SCI, bowel complications with frequent symptoms of obstipation(severe constipation), distension, abdominal pain, rectal bleeding, hemorrhoids, incontinence (involuntary urination), musculoskeletal complications such as osteoporosis, metabolic complications, immunologically mediated neuroinflammation, neurogenic bowel caused due to lack of neural control, spasticity, and pain which 80% of patients suffer from(Hagen, 2015)(Sezer, Akkuş, & Uğurlu, 2015). Spinal cord injury's pathophysiology involves several interrelated events, each facilitating another. In some instances, multiple events occur simultaneously and cause diverse, complicated symptoms, consequently rendering this illness difficult to treat.

B. Classification of spinal cord injuries

Classification of spinal cord injuries plays a vital role in diagnosing and treating a traumatic spinal cord injury. The method of classification of SCI was developed by International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). An ISNCSCI exam includes three scores: American Spinal Injury Association (ASIA) motor score, ASIA sensory score, and ASIA Impairment Scale grade. Each one of these, respectively grades muscle strength and movement, sensory function, and whether the injury is complete or incomplete. An ASIA score has grades A, B, C, D, and E, with A being the most severe and E the least. Grade A is when there is a complete loss of sensory or/and motor function; grade B is given when sensations are present but the motor function is lost below the point of injury; grade C is when the motor function below the point of injury is preserved and the ASIA motor score is less than 3; grade D is when the motor function below the point of injury is preserved and the ASIA motor score is 3 or above; grade E is when a patient has normal sensory and motor function (Health Central, 2019).

Spinal cord injuries are broadly classified into two groups: complete SCI which occurs when there is a total loss of motor and sensory function below the point of injury and incomplete SCI occurs when there is some function below the point of injury. Incomplete spinal cord injury is classified into 3 distinct syndromes. The first is central cord syndrome which makes up 15-30% of all traumatic cases. This syndrome affects the central part of the spinal cord, which is responsible for transmitting information between the cerebral cortex and the spinal cord (Health Central, 2019). It results in loss of motor function in the arms and legs, loss of sensation below the point of injury, and loss of bladder control (NIH, 2023). The second syndrome is Brown-Séquard syndrome which is usually the result of penetrating trauma like a bullet or knife wound causing the hemisection of the spinal cord (Health Central, 2019). It results in weakness, paralysis, and/or loss of stimuli detection on the side of the injury and loss of sensations of pain and temperature on the other side(Shams, S., & Arain, 2022). The third syndrome is anterior and posterior spinal cord syndrome, which is most common in nontraumatic SCI cases. Anterior spinal cord syndrome results in a complete loss of movement, pain, and pressure, but can detect sensations of light. On the other hand posterior spinal cord syndrome causes loss of sensations of light and sensations of pain, pressure, and temperature are preserved (HealthCentral, 2019).

C. Treatments for spinal cord injuries

The essential goals in the treatment and management of SCI are minimizing the primary neurological damage, and preventing secondary cord injury due to reduced or restricted blood flow, apoptosis, and biochemical and inflammatory changes. However, the current goal of treatment of SCI is to reduce secondary injuries and help restore normal neural functioning. To achieve this the primary treatments are pharmacological neuroprotection, early surgical depression and stabilization, and arterial pressure augmentation(Guo, Zhang, Zhai, & Xue, 2022). Treatment strategies vary according to the symptoms presented and the stage that they present themselves in. The protocol for the overall treatment of spinal cord injuries is standardized (See Fig.3).

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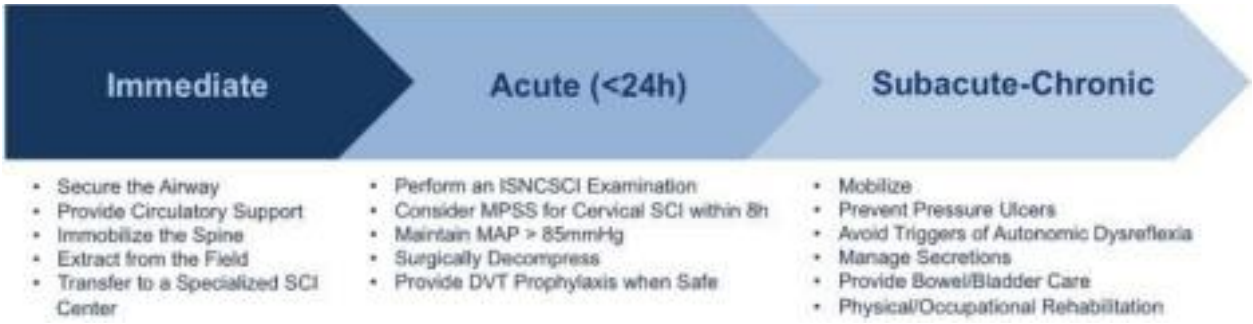

Fig 3: Standardized treatment for SCI. Reference: (Hachem, Ahuja, & Fehlings, 2017)

When SCI is in the primary stage, pharmacological-based treatment according to the patients' respective symptoms is given, and in the secondary stage, various combinations of therapeutic treatment involving the usage of neural tissues and neurotrophic factors are provided(Katari Venkatesh, Ghosh, Mullick, Manivasagam, & Sen, 2019). The foremost and most popular clinical treatment for spinal cord injury is surgical decompression, its goal is to relieve mechanical pressure on the blood circulation, thereby reducing restriction of blood flow(Rouanet, Reges, Rocha, Gagliardi, & Silva, 2017). It is crucial that it be performed within 24 hours of the injury as quicker treatment could reduce secondary complications.

Pharmacological-based neuro protections include riluzole which prevents stimulation of glutamate receptors by sodium channel blockade and although the FDA approved it as a treatment for amyotrophic lateral sclerosis it had not been approved for SCI, ketorolac has been shown to reduce neuronal death at the site of blood constriction which leads to improvement in the hindlimb motor function, minocycline modulates CNS immune cell, and prevents neuroinflammation and cell death, magnesium showed improved motor function scores after its treatment, methylprednisolone improves blood flow of spinal cord, and treatment of monosialotetrah-exosylganglioside showed neurological improvement after a year(Baptiste & Fehlings, 2007)(Katari Venkatesh, Ghosh, Mullick, Manivasagam, & Sen, 2019). Fampridine may restore the ability of axons to transmit electrical impulses; potassium and sodium channel blockade was shown to improve axonal conduction after the destruction of myelin, and both of these drugs have been shown to improve axonal conduction in the injured spinal cord(Baptiste & Fehlings, 2007). Another pharmacological-based neuroprotection is the administration of high-dose intravenous methylprednisolone sodium succinate (MPSS) in the acute stage of SCI injury but is very controversial as the suitability of it as a treatment option for neuroprotection has been questioned and the AANS/CNS SCI guidelines (2013) recommend against its use as its harm is outweighed by the potential benefits(Rouanet, Reges, Rocha, Gagliardi, & Silva, 2017). Other complications arising from SCI such as cardiac and respiratory complications are treated accordingly.

The main long-term non-pharmacological treatment option for SCI is rehabilitation, and although long and expensive, it can have significant effects on a patient's long-term health by helping patients to recover as much function as possible, prevent secondary complications, and help patients adjust to challenges that their injury possesses.Physical rehabilitation focuses on regaining and enhancing function and preventing complications. It includes strength training, cardiovascular-focused exercise, respiratory conditioning, and transfer or mobility training(Nas, Yazmalar, Şah, Aydın, & Öneş, 2015).

The past decades have shown various advances in neurosciences research into spinal cord injury. This has resulted in increased mortality rates of SCI patients, improved quality of life, and gives high hope for regeneration and functional restoration.

IV. OVERVIEW OF STEM CELLS

Stem cell research began 30 years ago when scientists were able to derive embryonic stem cells from early mouse embryos. Since then it has evolved and is considered the future of regenerative medicine and one of the most promising disciplines in the fields of modern science & medicine. This is because it has the ability to renew itself and differentiate to form multiple tissues and specialized cells, such as muscle cells, blood cells, and brain cells. It offers endless possibilities for life-changing treatments for dangerous diseases.

It provides hope for a future where it is possible to replace diseased cells, tissues, or organs and eventually

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reach normal function. This future is getting closer to reality as various research communities began to study the potential applications across multiple diseases such as neurodegenerative diseases and diabetes. Already stem cells are being used in treatment with success. The most established stem cell treatments are bone marrow transplants which are used to treat blood and immune disorders and skin cell grafting for burn victims as a replacement for the cells that have been damaged (EuroStemCell, 2023). Across the last couple of years, there have been various clinical trials based on the applications of stem cells, some of which have yielded results. For example, a patient with a skin disease (Epidermolysis Bullosa) saw signs of skin recovery after skin cell (keratinocyte) cultures of epidermal stem cells(Aly, 2020). Another patient with macular degeneration reported improvement in eyesight after the transplantation of patient-derived induced pluripotent stem cells that were made to differentiate into pigment epithelial cells of the retina(Aly, 2020). Unfortunately, as much as we now know there is so much more yet that we do not understand, from which type of cells are best for use to which method of transplantation will have the most successful results have still not been determined. There is also a lot of political debate and media coverage surrounding stem cell research which raises many ethical and religious issues and generates a great deal of public interest. This is due to the fact that human embryonic stem cell (hESC) research involves the destruction of human embryos, which has brought forth various ethical and religious concerns. However, the potential that stem cells holds cannot be ignored.

A. Classification of stem cells

The human body has 3 types of cells: somatic cells which make up the bulk of the human body, germ cells which give rise to gametes and stem cells which have the ability to divide indefinitely in a proper environment and have the ability to give rise to mature specialized cell types. Stem cells also possess plasticity, the ability to differentiate into cell types other than the tissues in which they are, but unfortunately, they only make up a very small percentage of the cells in the human body. Stem cells are classified into 3 types, all of which possess the ability to differentiate but exist in a development hierarchy, totipotent stem cells, embryonic stem cells, and adult stem cells. Totipotent cells, the most underdeveloped stem cells, have the ability to form all cell types of the conceptus including the entire embryo and its tissues. It is present in early mmmalian embryos and its lifespan is between the fertilization of the ovum and until the embryo reaches the four to eighth stage of development. Succeding this, the cell undergoes divisions to reach the blastocyst stage where they acquire a pluripotent identity after shedding the totipotent identity. Pluripotency is the ability to form several cell types of the three germ layers, ectoderm, mesoderm, and endoderm, but not the whole organism. Stem cells with a pluripotent identity are of 4 types embryonic stem cells, embryonic germ cells, embryonic carcinoma cells, and recently the discovery of a fourth class of pluripotent stem cells, the multipotent adult progenitor cell. These cells are acquired from the inner cell mass of the blastocyst which involves the destruction of the developing embryo. Following this stage, the cells undergo further differentiation leading to the loss of the pluripotency ability and the cells acquire multipotent ability -the ability to differentiate into a limited type of cells appropriate to their location. These cells are known as adult stem cells, which are responsible for the creation of homeostasis throughout the organism's lifetime. These are present in a metabolically quiescent state close to all the specialized tissues in the body. Stem cells are usually classified according to their location of origin. For example, stem cells of the gonad are the oogonia and spermatogonia (present in the ovary and testis respectively)(Aly, 2020; Bongso & Richards, 2004).

The major types of stem cells are embryonic stem cells (ESCs), induced pluripotent stem cells (IPSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs). embryonic stem cells are pluripotent and are derived from the blastocyst of the embryo. Their benefit of unlimited proliferation is outweighed by the risks: ethical problems, risk of immune rejection, unpredictable differentiation, and high risk of tumor formation. Induced pluripotent stem cells are also pluripotent in nature but are taken from fibroblasts, hepatocytes, circulating T cells, and keratinocytes of reprogrammed adult cells. The benefits of this include no ethical problems, low risk of immune rejection, and high accessibility. While as the losses of this cell are a high risk of tumor formation, risk of susceptibility to the original pathology of the patient, and genetic and epigenetic abnormalities. Mesenchyml stem cells on the other hand are multipotent and derived from adult tissues such as bone marrow, skin, blood, umbilical cord, etc.. The advantages of MSCs are no ethical problems, high accessibility, easy isolation methods, autologous cell generation, self-renewal capacity, and low risk of immune

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rejection. The disadvantage of MSCs, which is the risk of tumor formation, is outweighed by the advantages making it one of the more desirable stem cells. Neural stem cells are also multipotent and are derived from the embryo and human fetal brain and brain tissue of adults. The benefit is a low risk of tumor formation. On the other hand, the cons of NSCs are ethical problems, risk of immune rejection, limited differentiation, low self-renewal capacity, limited proliferation and expansion, limited availability, and difficult isolating methods. Hence the number of potential risks of NSCs makes using particular stem cells difficult(Aly, 2020; Bongso & Richards, 2004).

B. Stem Cell-based therapies

Stem cell-based therapies are defined as the treatment for a disease or a medical condition that revolves around the use of a type of viable human stem cells such as embryonic stem cells (ESCs), patient-derived induced pluripotent stem cells (iPSCs), and adult stem cells for autologous and allogeneic therapies(Aly, 2020). There are around 6,000 clinical trials based on stem cell research around the world(Aly, 2020). Stem cells have been researched for the treatment of various diseases such as ocular diseases, neurodegenerative diseases, diabetes, and dental diseases. Multiple clinical trials for stem cell-based therapies for ocular diseases are ongoing since the eye is an immune-privileged site, one of these showed that iPSCs-based autologous transplantation was safe and feasible. For the treatment of diabetes pluripotent stem cells (PSCs) are being considered for transplantation. In the field of dentistry, mesenchymal stem cells (MSCs) have been successfully isolated from human teeth and the ability to regenerate dental structures and periodontal tissues has been studied. Clinical trials have only recently begun and have not been completely evaluated, but stem cell-based dental and periodontal regeneration may soon be an available treatment(Aly, 2020; Bongso & Richards, 2004; Ikehara, 2013).

Stem cells based therapies have been targeted for neurodegenerative diseases. One disease is parkinsons: ESC cells and iPSC cells both cells gave the potential of obtaining an endless source of dopaminergic neurons, and protocols that mimicked the development of dopaminergic neurons succeeded in producing dopaminergic neurons similar to those present in the midbrain. Another neurodegenerative disease is multiple sclerosis (MS) where stem cell-based therapy is now exploring the idea of stopping the progression of the disease and reversing the neural damage. Unfortunately, many clinical trials for MS are still in the initial stages and are exploring the possibility of replacing damaged neuronal tissue with iPSCs-derived cells. There are multiple clinical trials surrounding stem cell-based therapies for amyotrophic lateral sclerosis (ALS) or Lou Gehrig's Disease, the first attempt used MSCs for transplantation in a mouse model, and results showed a decrease in the disease manifestations. According to this principle, various clinical trials are ongoing and have not shown any results. Stem cell-based therapies have also been used for spinal cord injuries, in which there was transplantation of different neural stem cells and oligo-dendrocyte progenitors. This has led to growth in the axons and increased neural connectivity, showing the possibility for nerve repair. However proof of recovered function has yet to be proved(Aly, 2020).

There are many hurdles in stem cell therapy that have yet to be crossed. Issues such as the ethical concerns of using human embryos and some of the transplantation models have formed tumors over time. Other challenges are how to use ESC and to reduce its contamination, to prevent the rejection of the cells by the recipient's immune system. Another challenge that arises is how to identify and isolate stem cells from tissue, and then induce their differentiation into the desired cell types (Aly, 2020; Ikehara, 2013). Some of the solutions for these issues have been hypothesized but are yet to see results.

V. OVERVIEW OF STEM CELL THERAPIES FOR SPINAL CORD INJURIES

Unfortunately, even with 1 million people across the world suffering from Spinal cord injuries with all of them having different severities of neurological deficits, there is still no complete cure. One of the many strands of interest that are being researched for a possible solution is stem cell-based therapies, which can help with neuroregeneration, an ability that mammals do not have. The main of stem cell research for the treatment of spinjal cord injuries is the regeneration and replacement of neurons and glia that have died soon after injury(Ronaghi, Erceg, Moreno-Manzano, & Stojkovic, 2010).

A number of clinical trials and experimental studies on stem cell-based treatments for SCI are being conducted

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across the world. However the clinical trials vary in the manner in which they are conducted, and there is no universal agreement on the best method for transplantation timing, cell dosage, cell type, and mode of transplantation (Yamazaki, Kawabori, Seki, & Houkin, 2020).

The research that has already been conducted has shown that transplanted cells display multiple neuro and vascular-protective effects, have the capacity to reduce inflammation, and are able to help with axonal regeneration, synaptic sprouting, and reducing glial scars.

The mechanism of using stem cells has been broadly classified into 3 groups: cell replacement is the transplantation of the stem cells into damaged neuronal or vascular cells; functional multipotency or also called the nursing effect occurs when the transplanted cells start secreting certain trophic factors to help reduce the neral damage; stem cell regeneration takes place when the stem cells transplanted activate the already present stem cells in the spinal cord (host stem cells), this causes the host stem cells to start differentiating (Yamazaki, Kawabori, Seki, & Houkin, 2020).

Most clinical trials target a particular stage of secondary stages of a spinal cord injury: acute (stem cell transplantation takes place a few days after the injury), sub-acute (stem cell transplantation takes place within 6 months of the injury), and chronic (stem cell transplantation takes place after 6 months of the injury). The stem cells that are majorlybeing used are mesenchymal stem cells (MSCs), NSCs, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs). The bulk of clinical trials focus on the chronic stage and uses Mesenchymal stem cells from the bone marrow, and are still in the first stages of research (no control group patients). In contrast, the majority of animal preclinical experiments are in the acute stage (Yamazaki, Kawabori, Seki, & Houkin, 2020).

The following passages give a brief overview of 3 clinical studies which have had significant success in mitigating the results of spinal cord injury and specifically increasing the overall neurological function in the patient and hence potentially increasing patient quality of life and decreasing the overall mortality rate.

A. Trial One: Significant Improvement of Acute Complete Spinal Cord Injury Patients Diagnosed by a Combined Criteria Implanted with NeuroRegen Scaffolds and Mesenchymal Stem Cells

To reduce/prevent maximum secondary damage, this clinical trial focuses on using stem cells in acute SCI patients. A biomaterial scaffold called NeuroRegen scaffold - a collagen scaffold consisting of ordered collagen fibers- was used, because collagen has proven to be useful for clinical use since it has low antigenicity, is an excellent biocompatibility, and is biodegradable. Mescycmal stem cells (MSCs) were used as it had previously proved that is could decrease cell apoptosis, promote angiogenesis and reduce lesion size in central nervous system injuries, and modulate the host's immune microenvironment, and were considered promising for cellular respiration, inducing neural regeneration and functional recovery (in animals). MSCs cells taken from the umbilical cords of human donors were placed inside the NeuroRegen scaffold which was prepared from a bovine aponeurosis and then placed at the injury site, to repair damage.

In Preclinical trials, these cells were implanted in acute and chronic canine SCI subjects. It showed a result of increased hindlimb locomotor recovery by reducing scar formation and inducing neural regeneration. Locomotion improvement was observed after 3 months of implantation surgery. For the clinical trials, two patients with acute SCI were used, with injury at thoracic and cervical respectively. Unfortunately, ASIA scale can not accurately predict the score of a patient in the acute stage of SCI. This is because of spinal shock which means that the nervous system is unable to transmit signals effectively. Spinal shock starts a few minutes after injury and usually lasts for several days but sometimes can continue for a few weeks. But approximately it was predicted that the patients had an ASIA grade A score.

The surgery took place 8 takes after injury. First stimulation electrodes of electromyography were used to detect neural signaling, and it showed that both patients had been completely injured. No obvious post-surgery symptoms were observed and no neural signaling was detected. In thoracic patient, who before surgery had complete loss of function below T11, showed recovery of sensory function and muscle contraction after three months; at six months the sensory score increased from 72 to 84, and was able to walk under the support of a brace; at nine months the patient was able to recover bowel and bladder sensation; at 12 months was able to voluntarily walk with the hip under the help of a brace.

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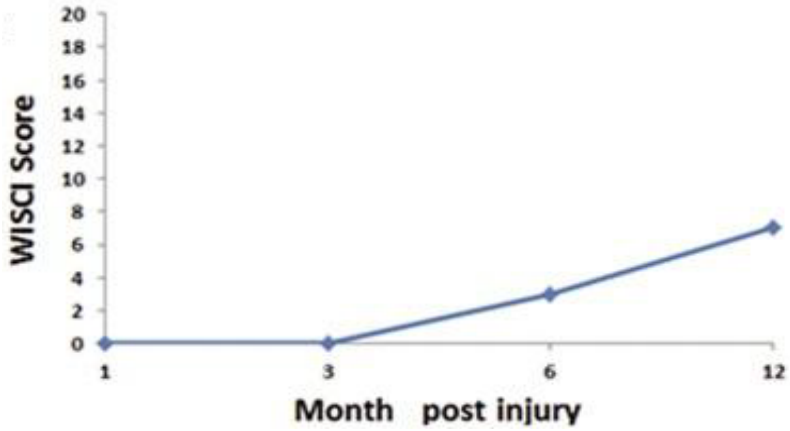

Fig 4: Shows the recovery rate of patient 1 in the months following the transplantation.

Reference: (Xiao et al., 2018)

In the cervical patient, sensory recovery began after two months; after three months there was movement in the lower extremities; at 6 months patients sensation increased to S2 on the left side and T10 on the right side, was able to move lower legs and toes, and the motor score increased from 0 to 18 on the left side and 0 to 22 on the right side. At nine months sensation level increased to S5 on the left side and the sensory score increased from 46 to 110; at 12 months the patient regained function of the bladder and bowel and felt the sensation of deep anal pressure. In the end, both patients' ASIA scores were grade C. There was a similar pattern of recovery in animal and human trials which indicates that the scaffolds may cause neural differentiation of endogenous neural stem cell tissue. These results suggest that the recovery shown in patients in the clinical studies was induced by functional transplantation (Xiao et al., 2018).

The result indicates that this manner of transplant may have potential success in the long term, but need to be researched further and trialed on a larger treatment group before accurate conclusions can be reached.

B. Trial Two: Complete Spinal Cord Injury Treatment Using Autologous Bone Marrow Cell Transplantation and Bone Marrow Stimulation with Granulocyte Macrophage-Colony Stimulatin Factor: Phase I/II Clinical Trial

This trial uses bone marrow cells taken from the iliac bone of human donors, which under specific conditions can differentiate into mature neurons or glial cells. Bone marrow cells have been shown to improve neurological problems by producing neural cells. There will also be an injection of granulocyte macrophage-colony stimulating factor (GM-CSF) under the skin after surgery for 5 days continuously and once a month for over 5 months. GM-CSF was used because it can decrease neural apoptosis and stimulates microglial cells which causes the increase of brain-derived neurotrophic factor (BDNF) which in turn promotes the development of immature neural cells into mature neurons (Hromadkova et al., 2020).

All patients had ASIA grade A. They had already had successful spinal decompression and stabilization. The patients were dived into 3 groups 14 days after initial spinal surgery: acute (<2 weeks), subacute (2–8 weeks), and chronic (>8 weeks). A control group of 14 patients out of a total 53 were established. Patients in this group did not get the transplantation of stem cells or the injections of GM-CSF, while the rest of the patients in the study did. 48 out of 53 patients were involved in the 10-month follow-up.

Patients in the treatment group experienced higher degrees of fever (but this did not increase the mortality rate), and 20% of the patients developed neuropathic pain (it was mainly confined to subacute and chronic patients). One patient in the chronic stage experienced loss of motor function but regained the function after 1 month. The result of the trial showed 29.5% of patients in the acute stage showed neurological improvement and a change of ASIA score from grade A to B or C. 33.3% of patients in the subacute stage showed neurological improvement and an increase in ASIA grade from A to B or C. however the patients in the chronic group did not show any observable changes in neurological function (Yoon et al., 2007). This suggests the treatment with certain adjustments may produce significant results in the future for subacute patients of groups with less than 2 weeks and 2 to 8 weeks after initial spinal surgery.

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Adverse events	Treatment group (%) (n = 35)	Control group (%) (n = 13)	p
Fever	22 (62.9)	3 (23.1)	.022
Abdominal discomfort	7 (20)	7 (53.8)	.034
Numbness or tingling sensation	6 (17.1)	4 (30.8)	NS
Facial flushing or rash	5 (14.3)	1 (7.7)	NS
Headache	3 (8.6)	1 (7.7)	NS
Constipation	3 (8.6)	3 (23.1)	NS
General ache	3 (8.6)		NS
Rigidity	3 (8.6)		NS
Transient neurologic deterioration	1 (2.9)		NS
Spasticity	1 (2.9)		NS

Abbreviation: NS, not significant.

Fig 5: Adverse effects of patients in the trial. Reference: (Yoon et al., 2007)

C. Trial 3: Treatment of chronic spinal cord injured patients with autologous bone marrow-derived hematopoietic stem cell transplantation: 1-year follow-up

This trial used autologous blood marrow-derived progenitor which can only differentiate into a specific cell type) stem cells in chronic patients. Bone marrow was withdrawn from the iliac crest to obtain mononuclear cells. The stem cells were injected into the injury site and then covered with stem cell storage material (gel foam), then additional stem cells were injected into the gel foam. No immune suppressors were provided as the cells were obtained from the patient. The transplantation took place 6 months after SCI happened.

Patient 1 was a 37-year-old female with a fracture and dislocation of C6-7. Had minimal movement of fingers and arms, was paraplegic, spastic, and had a loss of sensation btw C3 and C5, and could not feel pain below C5. 72 hours after; surgery spasticity disappeared and sensation improved between Th 1- 2 levels. 3 weeks later, sensation improved to Th10, the patient could contract back muscles and achieve a crawl position. 3 months later, the patient was able to maintain a sitting position without help. 6 months later, the patient could stand with help. 9 months later, the patient could swim without help. ASIA level increased from A to C.

Patient 2 was a 19-year-old female with a Th8 fracture. She was paraplegic with 0/5 muscle strength in the lower extremities and spasticity in the lower extremities. 3 weeks after surgery spasticity disapeared, sensation improved to Th12, muscle strength was 1/5, and could achieve crawl position. ASIA was grade C after 1.5 months and remained the same.

Patient 3 was a 40-year-old female with C6-7 and Th1 fractures. She was paraplegic, could not feel pain below C5, had a muscle strength of 0/5 at the lower extremities, and spasticity in the lower extremities. 3 weeks after surgery spasticity disappeared and her sensation level had improved to Th10 level. 1.5 months after surgery she could achieve a crawl position and maintain that position. ASIA belgrade changed to C after 2 months, grade remained after a year.

Patient 4 was a 20-year-old male with a fracture at C4-5-6. He had minimal movement in wrists and no movement in fingers and arms, was paraplegic, extremely spastic, and could not feel pain below C4. 3 weeks after surgery spasticity at the lower extremities decreased slightly and his sensation level improved to C6 level. At 1.5 months he could move his right thumb. ASIA at the end was grade C.

Patient 5 was a male in his 20s with a dislocation and fracture of C5-6. His arm and wrist movements were close to normal but had no motor function in his fingers. He was paraplegic, had spasticity in his lower extremities, and had no motor function below C4. Immediately after the operation, he complained of a slightly decreased sensation in his body and slightly decreased wrist and arm movement. Movement retired to before state after 2 weeks. After 3 weeks spasticity disappeared and there was an increased sensation, especially between C4 and T3. ASIA B was achieved after 2 months

Patient 6 was a 30-year female with a fracture and dislocation of C5-6. Had minimal movement in her arms and

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no movement at her wrists and fingers. She was paraplegic, extremely spastic, and had loss of sensation below C4. 72 hours after stem cell transplantation her spasticity decreased and her sensation level improved to C6 level. After 96 hours she was able to move her left wrist slightly. After 3 weeks her sensation level had improved to the Th4 level, and could move her wrists and arms, contract her back and hip muscles, and could achieve a crawl position. Was declared ASIA grade C at the end.

Patient 7 was a 30-year-old male with a fracture at C5. He was slightly spastic in the lower extremities and had a loss of motor functions below the Th3 level. Three weeks after the operation his sensation level had improved to the Th4 level. ASIA was grade B in 1 month of operation,

Patient 8 was a 17 female with a fracture of the Th10. She had a total loss of sensation below Th9, was paraplegic, had a muscle strength of 0/5 at the lower extremities, and spasticity at the lower extremities. Three weeks after surgery her spasticity at the lower extremities had decreased, sensation level had improved to the Th12 level and muscle strength was 1/5 at the left hip flexors and in the abdominal muscles. ASIA grade C was achieved in the end.

Patient 9 was a 40-year-old male with a fracture of the Th11. He had a total loss of sensation below Th10, was paraplegic, had a muscle strength of 0/5 at the lower extremities, and was slightly spastic at the lower extremities. Three weeks after the operation, his spasticity at the lower extremities had decreased and his sensation level had improved to the L1 level. ASIA B was scored in 3 weeks, and ASIA grade C was reached in 6 months.

In conclusion, all patients were initially ASIA grade A and paraplegic and had spasticity in the lower extremities. Most had a loss of motor and/or sensory function below the site of injury.

	Case study								
	1	2	3	4	5	6	7	8	9
Age (years)	37	19	40	20	20	30	30	17	40
Sex	F	F	F	M	M	F	M	M	M
Trauma level	C6–7	T8	C6–7	C3–6	C5–6	C5–6	C5	T10	T11
Time since injury (years)	17	2	2	2	2	10	7	2	2
Symptoms	S	S	S	S	M	S	M	M	M
Pre-operative ASIA scale	A	A	A	A	A	A	A	A	A
Pre-operative neurologic rehabilitation	+	+	+	+	+	+	+	+	+
Pre-operative MRI	+	+	+	+	+	+	+	+	+
Pre-operative stabilization procedure	+	+	+	+	+	+	+	+	+
Operation	CL	TL	CL	CL	CL	CL	CL	TL	TL
Number of transplanted cells millions	50	37	21	20	24	28	29	40	67

F, female; M, male; S, severe; M, moderate; CL, cervical laminectomy; TL, thoracic laminectomy.

Fig 6: Summarises results of the trial. Reference: (Deda et al., 2008)

Results of this trial showed that there was an increase in ASIA grade from A to B or C. There was also a significant increase in neurological function and spasticity in the lower extremities decreased or disappeared, in all of the patients in the study (Deda et al., 2008).

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The significant positive result that this trial shows, displays that the study has true potential for possibly being an ideal treatment method` and should be further studied.

Table 1.Comparison of all three case studies

Case:	Trial 1	Trial 2	Trial 3
No. of Patients:	2	53	9
Pre-operative ASIA level (avg):	A	A	A
Stage of secondary injury:	Acute	Sub-acute	Chronic
Type & mode of stem cells:	NeuroRegen scaffold with MSCs cells from umbilical cords of a human donor. Was injected at the site of injury.	BMC from the iliac bone of human donors with a series of subcutaneous injections of GM-CSF. Was injected at the site of injury.	Autologous BM-derived progenitor withdrawn from the iliac crest. Injected into the injury site, covered with gel foam, then additional stem cells were injected into the gel foam.
Post-operative ASIA level:	C	A,B or C	B or C

VI. CONCLUSION

In the studies observed above there was a significant and distinct improvement in neurological function in Case Studies 1 and 2. While Case Study 2 was more controversial and required significant alteration before it can clearly be defined as successful. Before cases 1 and 2 can definitely be proved it requires a trial with a larger group of patients. If the results found in the first trials prove correct for the second larger trial then this can broadly be used for SCI patients under the same conditions as in the trial. It also shows that both autologous BM-derived progenitor cells and MSCs cells from the umbilical cord with the help of NeuroRegen scaffold may have particular benefits and should be researched further for the possible uses of this method, in different neurological diseases where the regeneration of neurons is desired.

If the increased level of progress continues then in a few years we may be able to have a defined treatment for spinal cord injuries which can effectively treat nerve damage using stem cells. With significant steps being made in the treatment of spinal cord injuries through stem cell-based therapies and other methods, the question of how spinal cord patients across the world can have access to these new innovative treatments arises. At the moment in low-income countries, medical services cannot prevent secondary damage that is preventable in high-income countries. Therefore as vital as advancing current medical knowledge and creating new innovative treatments is, it is also essential to see the development of countries across the globe and ensure a standard of medical care is established and made affordable and available to all. This can only be achieved with worldwide support, funding, and by providing all the help we can alone can give.

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