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Review Article

Effect of Various Treatment Modalities After Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is a devasting neurological condition producing physical dependency, morbidity, psychological stress and financial burden, Spinal cord injury is characterized by the degradation of motor, sensory and autonomic functions either because of wholly or partially damage in the spinal cord because of trauma. Its a debilitating neurological condition with socio economic impact on affected individuals and the health care system, It completely changed subjects life because it's a life long treatment and loss of income and patient completely depend on others. According to Ara Z., *et al.* 2022 SCI is a life threatning process and it greatly effects subjects' quality of life and families, In 1700 BC in an Egyptian surgical papyrus, they describe the frustration of health care professionals in treating a severe spinal cord injury, the Papyrus reported spinal fractures as a ''disease that should not be treated''.

Most of these studies approach a patient with acute spinal cord injury (ASCI) in one of four manners: corrective surgery or a physical, biological or pharmacological treatment method. clinically, we only provide supportive care for patients with spinal cord injuries. By combining these treatments, researchers attempt to enhance the functional recovery of patients with spinal cord injuries. Advances in the last decade have allowed us to encourage the development of experimental studies in the field of spinal cord regeneration.

Keywords: SCI; Neuroregeneration; Antioxidant; Complete/Incomplete Paraplegia; Decompression

Introduction

Damage or trauma to the spinal cord leads to a total or partial loss of sensory or motor function and is referred to as spinal cord injury (S.C.I.). An imbalance between the production of reactive oxygen species and the levels of antioxidant defences, causing neuro-inflammation and oxidative stress, is the peculiar characteristic of S.C.I. It primarily affects an individual's quality of life, functional status, and social independence. It is the most serious and difficult traumatic neurological condition for clinicians to treat. It's irreversible with high economic and social costs; two major categories of S.C.I. are S.C.I. caused by external physical impact and non-traumatic S.C.I. The primary cause of S.C.I. is trauma, but tumours, infection, and vascular lesions or iatrogenic procedures are the other major causes.

Life-life severe dysfunction as complete/incomplete paraplegia or tetraplegia occurs due to S.C.I. Sometimes, it's life-threatening because of severe complications resulting from an injury such as pneumonia, severe decubitus, and urinary tract infection. Immediate physical damage to the spinal cord due to the laceration, contusion, compression, and contraction of the neural tissue is referred to as primary injury [1]. Only structural damage occurs during primary injury. It is an irreversible and temporal process; in this case, spinal cord parenchyma is direct damage due to vertebral fracture and ligament avulsion [2]. Due to primary injury, there is dysfunction of blood supply in the cord [3]. Long term degradation of spinal neural tissue is due to inflammatory and secondary sequelae following primary injury, further influenced

by secondary injury. Specific secondary trauma or outcome of the primary injury include changes in local ionic concentrations, reduction in spinal cord blood flow, loss of regulation of local and systemic blood pressure, blood-brain barrier breakage, puncturing of serum protein into the spinal cord, lipid peroxidation/free radicals production, accumulation of neurotransmitter, imbalance of activated metalloproteinases, the occurrence of changes in inflammatory responses of chemokines and cytokines, apoptosis, excitotoxicity, calpain proteases etc. are different responses that lead to demyelination, ischemia, necrosis, and apoptosis of spinal cord tissue [4]. Primary and secondary mechanism injury gives rise to S.C.I.

In most cases, S.C.I. leads to paralysis and death [5]. Globally, over two million people live with S.C.I. trauma, including physical, social, psychological, and emotional impairments that often extend beyond affected individuals to their families, friends, employers, community, and health care system. The average annual incidence of S.C.I. in India is 15,000, with a prevalence of 0.15 million. (Rehabilitation Council of India. Spinal Cord Injury 2019 Jan 16). According to the World Health Organization (WHO), in developing countries, including India, the cases of S.C.I. is increasing day by day, so the health care burden due to S.C.I. is almost similar to that in the developed world**.**

The total number of people around the globe living with S.C.I. is increasing day by day due to rising populations, and geographically around the world, the major reason for the injury is road traffic accident and fall from a height. To reduce it, improvisation in road safety measures and prevention of falls must be the priority. [6]. One U.S. study demonstrates that the mean age of patients having S.C.I. in 1993 was 40 years, which exceeds 50 years in 2012. At the age of ≥ 65 years, there is an increase in injury due to secondary falls. [7], This trend of injury is similar in other high-income countries in the case of both S.C.I. and traumatic brain injury (T.B.I.). [8]. In his review, Yi Kang., *et al.* [9] enumerated that due to the expansion of human activities, the incidence of S.C.I. has extended, and it varies by region and country. The ratio of the male subject is more in comparison to females, and the patient's average age has also increased in the case of S.C.I. Traumatic spinal cord injury worldwide is approximately 700,000 individuals per year [10-11]. The incidence of traumatic S.C.I. (TSCI) per year in Québec, Canada, was approximately 10.6-22.6. [12]. In developed countries, The male: female ratio ranged from 1.10:1 [13] to 6.69:1 [13], whereas in non-developed countries, this ratio varies between 1.00:1 [14] to 7.59:1 [15], Labourers, farmers and the unemployed were three classes at high risk of S.C.I. injury [16]. High falls are primarily common in workers, resulting in thoracic and complete injury, while cervical and incomplete motor dysfunction results from low falls. The thoracolumbar spine injuries are more common, as this segment is more mobile than the dorsal or lumbar segments.

In northeast Indian population, the most common reason for spinal injury is to fall from height, followed by motor vehicle accidents. The most affected age group in their population is 20-39 years, followed by 50-59 years. The cervical spine (52.63%) was the most commonly injured vertebrae, followed by the thoracic (19.29%) spine. The C5-C6 level fracture-dislocation is commonest in cervical spine injury. Spinal injuries epidemiology differs somewhat from Sikkim and North-eastern India from other developing countries and other Indian states. Here in the younger population, road traffic accidents are the leading cause whereas fall from height is the main reason for the injury in the elderly group [17].

Due to S.C.I., between 250 000 and 500 000 people worldwide suffer. Because of the low global gross domestic product (G.D.P.) (~ $4000) as compared to the worldwide economy (~ $13,100), the scenario of S.C.I. is very challenging in India. Due to a lack of proper infrastructure and monetary constraints, it becomes difficult in India to access all components needed for S.C.I. management at comprehensive centres [18]. The current status of occurrence of S.C.I. both regionally and worldwide need novel treatment strategies to meet this harsh condition that must be beneficial and cost-effective in the regeneration of the damaged part of the spinal cord. Prevalent S.C.I. treatment strategies include anti-inflammatory medications, decompression surgeries to stabilize the spinal column and good supportive management for preventing secondary injury.

Numerous classification systems have been developed to characterize these fractures and their prognostic and therapeutic implications. Depending on the mechanism of injury, thoracolumbar injuries can be of different types, such as compression fractures, fracture-dislocations, burst fractures, translational injuries, rotational injuries and fractures with distraction injuries. Out

of these, compression fractures and fracture-dislocations are common. The clear exposition of pathological change and its relation to neurological change in spinal cord injuries remains the basis of all care. The spinal injury with neurological involvement shows a galaxy of pathological changes, ranging from extradural haemorrhage with petechial haemorrhages within the cord to gross dehiscence of the neural tube and Dura with evidence of cord crushing, central necrosis, shredding of nerve roots. Most thoracolumbar injuries present with both upper motor and lower motor neuron manifestations. The increasing incidences and, unfortunately, poor prognosis in neurological recovery in spinal cord injury (S.C.I.) have severely exposed the limitations of conventional management in this group of patients. Despite tremendous efforts worldwide, the improvement in neurological status is still unpredictable, and many resources continue to be invested in this aspect with little success. It has long been believed that intrinsic repair is quite restricted after the spinal cord is injured because neurogenesis rarely occurs in the central nervous system (C.N.S.). The neuronal cells are the most modified cells of the body, so they have very little or no power of differentiation. So, after any injury, they undergo degeneration without any repair.

As we know, it's a grievous condition and affects the quality of life of a subject and enduring permanent disability in the subjects; to date, no perfect treatment modality has been developed that helps in neurological recovery in S.C.I. In comparison to the peripheral nervous system, the regenerative capacity of the C.N.S., specifically the spinal cord, is limited due to the availability of a fixed number of regenerative cells and restricted plasticity. That's why when S.C.I. occurs, there are several hindrances in neurological recovery. [19]. Several treatments, from surgical intervention to nutraceutical strategies, focus on overcoming several neuronal regeneration obstacles. S.C.I. accounts for a small proportion of all injuries, but associated consequences make it one of the most life-changing injuries. Recently many therapeutic approaches have been developed to get rid of this life-changing injury, but few have progressed from laboratories to actual clinical practice [20]. For acute and chronic stages of S.C.I., there is a great demand for non-invasive, safe, feasible treatments.

Therapeutic possibilities

Around 1700 BC in an Egyptian surgical papyrus that Edwin Smith translated; they demonstrated the frustration caused by this irreversible disease; they told about spinal fractures were a "disease that should not be treated" (The Edwin Smith surgical papyrus. Chicago: University of Chicago Press; 1930) [21]. Several studies have been performed to identify better effective S.C.I. treatments over the last two decades. The treatment of acute S.C.I. patients was approached through these four manners, i.e., corrective surgery or physical, biological and pharmacological treatment methods**.**

Surgical techniques

Timing of surgery

To get rid of mechanical pressure in S.C.I. to reduce spinal cord compression and ischemia and optimize the local environment for neurological recovery, surgical decompression time here plays an important role. In one of their animal model studies, Batchelor PE., *et al*. [22] state that persistent spinal cord compression results in ischemia and exacerbates the secondary injury cascade after the initial trauma. Following these preclinical results, Fehlings MG., *et al*. [23] performed a prospective cohort study in subjects with cervical S.C.I. and observed two-grade improvement in ASIA impairment scale grade at six months follow up in a group with early decompression (< 24h after S.C.I.) in comparison to the late decompression group (≥ 24h after S.C.I.).

Many previous studies have reported improvements in A.I.S. grade and ASIA motor scores after early surgery (≤ 24h after S.C.I.), especially in cervical level injuries [24]. Grassner L., *et al*. [25] in one of their retrospective studies on subjects with cervical S.C.I., showed that subjects who underwent surgery within 8 hours of injury had better improvements in SCIM and ASIA scores at one year of follow-up after S.C.I. Many recent publications support early surgery's effectiveness, including the American Association of Neurosurgical Surgeons (AANS) and Congress of Neurological Surgeons guidelines and the current AOSpine guidelines [26].

Surgery plays a vital role in reducing additional neurological injuries. It helps in spinal alignment, nerve decompression and stabilization of the spine; using improved implant materials allows the stabilization of unstable fractures in reconstructive surgeries. Two significant benefits of surgery are to suppress further damage and help in rehabilitating patients earlier [23]. More substantial recovery was observed in patients who underwent early surgical decompression than subjects who underwent late decompression surgery one year after spinal injury. Improved Sensory-motor

score recovery is better in subjects who underwent surgical decompression within 24 hrs after S.C.I. The first 24-36h after injury represents a crucial time window for optimal neurological recovery with decompressive surgery following acute S.C.I. In one of the studies on decompression surgery, which was performed on 77 subjects with follow up assessment of 5 years by Anjarwalla., *et al.* [27], to determine the long term outcome concerning pain and physical function. They reported that back and leg pain was sustained for one year with improved physical function.

Physical means

To minimize secondary spinal cord damage, physical approaches are accessed as a better treatment method. Hypothermia, hyperbaric oxygen and exercise, particularly on a treadmill, are the most studied technique under physical means. Most studies have shown the beneficial effect of local cooling by perfusion or irrigation with hypothermic saline. However, this cooling therapy prevents potassium loss, such as in steroid therapy. This technique works on the principle that low temperature protects the central nervous tissues from hypoxia and ischemia. However, this technique is challenging due to its high mortality rate [28].

tudies have shown that after S.C.I., Hyperbaric Oxygen Therapy (HBO) treatment prevents oxidative damage to the spinal cord. Many studies on an animal model of S.C.I. have demonstrated the neuroprotective effect of HBO, as it downgraded the overproduction of tumor necrosis factor-α (TNF-α) and SCI-induced interleukin (I.L.)-1β [29]. It also significantly alleviates the number of glial cells line-derived neurotrophic factor- and vascular endothelial growth factor (VEGF)-positive cells and spinal cord IL-10 production [29]. In a current metanalysis on R.C.T. by Huang, Liyi., *et al.* [30], a total of 1746 studies were identified by them in which 11 studies were included involving 875 participants, and they concluded that hyperbaric oxygen therapy might improve sensory, motor function, as well as psychology after S.C.I., compared to conventional treatment. In contrast, it needs a large sample size and more R.C.T. to prove it.

Pharmacological therapy

Pharmacology plays a crucial role in treating S.C.I.; the medication can play an essential role in treating secondary S.C.I., as many experimental and clinical trials prove. Corticosteroids and gangliosides are already approved for human use.

Methy-prednisolone

To date, Methyl-prednisolone (M.P.) had not shown clinical significance in cases of S.C.I.; when administered intravenously at a very high dose of 35 mg/kg [31]. In one of the clinical trials of the National Acute Spinal Cord Injury Study I (NASCIS I), it was observed that when a high dose of M.P. was administered in S.C.I. subjects (1,000 mg IV bolus and daily after that for ten days) and standard-dose M.P. groups (100 mg IV bolus and daily after that for ten days) then after six weeks or six months after injury, no difference in neurological recovery was observed beside it in high dose group wound infection was seen to be more common [4]. To overcome the problems that arose due to this drug's side effects in one of their studies, Chvatal and colleagues showed its regenerative effect, protective effect, and functional outcome after applying it topically encapsulated in poly-lactic-co glycolic acid (PLGA) nanoparticle formulations at the injury site [32], In one of their reviews, Hirotaka Chikuda., *et al.* [33] demonstrated that subjects (3508 cervical S.C.I. patients, including 824 on high doses of methylprednisolone) had significant complications such as gastrointestinal ulceration/bleeding; however, its high dose administration is not associated with an increase in mortality.

Michael G. Fehlings., *et al.* [34] in one of their systematic and meta-analysis, demonstrated that when methylprednisolone sodium succinate was administered within 24 hrs of postinjury has no relevant impact on long-term neurological recovery when all postinjury time points are considered. In contrast, within 8hrs of injury, its administration showed an additional 3.2 points of motor recovery compared with patients receiving placebo or no treatment. Liu Z., *et al.* [35], have reported that in the case of acute traumatic S.C.I., high dose administration of methylprednisolone does not improve neurological outcomes despite increasing the risk of adverse events. Much work has been done with various secondary injury inhibitors, such as estrogen, in the hope of superior protection in secondary injury. Its analogues have been used in the case of the rat model to protect cells in culture and improve outcomes. In case oligodendrocytes [36], microglia, and neurons [37]. estrogen helps in preventing apoptosis, suppress activation of cysteine proteases, including calpain [36], in addition, it helps in attenuation of VEGF and upregulation of aquaporin [38]. A retrospective population-based cohort study was performed in South Korea in 2019 to study the prescription rate

and complications related to methylprednisolone therapy. Korean HIRA data between 2007 to 2017 were reviewed, and patients were examined by two categories, i.e., M.P. group vs non-MP group. The M.P. prescription rate was highest in 2012 (76%), and it continued to decrease after that and was lowest in the year 2017 (41%). But major complications in the M.P. group was pneumonia (OR 1.8, 95% CI, 1.62-2.0), G.I. bleeding (OR 1.2, 95% CI, 1.05-1.38), and U.T.I. (OR 1.68, 95% CI, 1.53-1.84), as well as patients also have higher hospitalization period who were on M.P. therapy.

Effect of Secretory Leukocyte Protease Inhibitor

Due to primary injury, there is dysfunction of blood supply in the cord due to breakdown of blood spinal cord barrier (BSCB), because of which spinal cord undergoes ischemia-reperfusion injury and oxidative stress [39]. A recent study by Renzhe Tang., *et al*. [40], demonstrated the protective role of Secretory Leukocyte Protease Inhibitor, which helps improve the S.C.I. by inhibiting the activity of the inflammatory signalling pathway, which releases a large number of inflammatory factors that can affect tissue repair. Hence, SLPI suppresses the Nuclear factor kappa beta (NF-κB) signalling pathway by binding to the tumor necrosis factor-αand interleukin-8 (IL-8) promoter region. In addition, due to its inflammatory anti-bacterial properties, SLPI promotes reducing secondary injury and other complications during S.C.I. and helps in wound healing.

Role of gangliosides

Several studies have explored the use of drugs in the case of S.C.I. treatment, including gangliosides, but their research is limited to the animal model; these studies need to be extrapolated as a therapy in the human model. Gangliosides are found in high concentrations in central nervous system cells. It forms a major cell membrane component and is located in the outer leaflet of a bilayer of the cell membrane, as it is a complex glycoprotein. However, its function is almost unknown, whereas, from studies, it is confirmed that they help in neuronal sprouting and helps in the regeneration of damaged nerve tissues. Recently in of their placebo double-blind, randomized trial study conducted on 37 patients,11 with thoracic injury and 23 with cervical injury completed the test drug trial intravenously 100 mg of GM-1 sodium salt or placebo was administered per day for 18 to 32 doses, with the first dose taken within 72 hours of the injury) and a one-year follow-up period. Neurological recovery was assessed through the Frankel scale and American Spinal Injury Association (ASIA) [40], They concluded that GM-1 enhances neurological recovery and neuronal function in a one-year follow-up. Geisler FH., *et al.* [41] conducted R.C.T. on 34 patients with acute S.C.I. to estimate the efficacy of monosialotetrahexosylganglioside sodium (GM-1). He reported that GM-1 treated group has significant improvement in neurological recovery with the usage of GM-1.

In a recent study conducted Sperling., *et al.* [42] on male rats with S.C.I., they were divided into two groups one group was administered 5 mg/kg galantamine (Galantamine is a tertiary alkaloid and reversible, competitive inhibitor of the acetylcholinesterase (AChE) enzyme) intraperitoneally for five days; it was reported that in comparison to control group galantamine group rats have higher locomotor activity when assessed thru B.B.B., and increased percentage of N.F.M. positive cells at six weeks post-injury when considered through flow cytometry. In contrast, the lesion size was reduced, and increased tissue survival was observed.

Ursolic acid

Ursolic acid proves to be effective in attenuating muscular atrophy and promotes signalling pathways for protein synthesis because it's an anabolic compound; it is injected intraperitoneally once per day [43]. One of the studies on animal models proved that treatment with ursolic acid after an injury helps reduce atrophy by > 50% in the first seven days [43]. Whereas combined treatment of ursolic acid administration and physical activity allows for a more significant increase in muscle mass, as well as help in reducing the expression of MuRF-1 and MAF-bx proteins, as well as causing a reduction in visceral adipose tissue.

Acetoside

An intramuscular injection also proves the best treatment in getting rid of muscular atrophy. In one of the studies, Kodani A., *et al*. [44], demonstrated that cultured skeletal myocytes treated with acetoside display proliferation and higher axonal growth than controls. Improved locomotor scores at 31-, 55-, and 62-days post-injury were also recorded in mice treated with acetoside.

Cethrin

Rho signalling pathway is a significant barrier in axon regulation, and after S.C.I., this pathway is upregulated, hindering axon regeneration [45]. A toxin produced by bacteria clostridium

botulinum called c3 transferase has the property to block rho-mediated inhibition of axonal growth by blocking rho an (a type of rho protein) and promoting neuronal development [46]. The result of a phase I/IIa clinical trial of a c3 transferase, ba-210 (trademarked as cethrin), was published by, Fehlings., *et al.* [47], when a single dose of the drug (0.3 to 9 mg), a permeable material, was applied at the time of decompressive surgery of S.C.I. at dura matter, with acute complete injury of more than seven days on 48 patient then increased motor recovery and ais grade conversion from ASIA scale A to ASIA scale C or D at one year follow up was observed in approximately 6% of the thoracic spine injury patients and 66% of cervical spine injury, in spite that no serious events were reported regarding the drug.

Magnesium with polyethylene glycol

Magnesium is antagonistic of *N*-methyl-D-aspartate (NMDA) receptors which helps in reducing inflammation and excitotoxicity. After traumatic spinal cord injury, it has been observed clinically and experimentally in human blood and brain of animals that Magnesium is continuously depleting. This depletion is the major cause of poor neurological outcomes in humans and animals. The study by Kahraman., *et al*. [48] demonstrated that in the serum of T.B.I. patients significant decline of Mg^{2+} levels was measured and is linked to the severity of T.B.I. Previous clinical studies showed that it's a multifactorial pharmacological intervention with proven safety, but it has been yet to be investigated. Interestingly, it was proved clinically that Mg^{2+} in P.E.G. formulation is currently available treatment in the case of S.C.I. and is more effective than methylprednisolone [49]. André Sperl., *et al*. [50] in one of their Prospective Clinical Observer Study showed the role of Magnesium in the Secondary Phase After Traumatic Spinal Cord Injury, In their study, they enrolled 29 patients with TSCI and at different 11-time points, blood samples were drawn over three months after that magnesium quantification was performed. Patients were divided into two groups, i.e. (G1, n = 18) and (G0, n = 11) with or without neurological remission; they observed that there is a slight decrease in the magnesium level during the first four h after injury, after that its status remains almost unchanged in G1. In contrast, in G0, they observed a continuous increase in Mg level during the first seven days after injury. At the seven days, Mg concentrations in both groups were significantly different. Significant differences were detected between patients in G1 that presented an A.I.S. (ASIA Impairment Scale) conversion of 1 level versus those with more than 1 level ($p = 0.014$, G1 A.I.S. imp. = +1 > G1 A.I. imp. > +1). Low and decreasing levels of Mg within the first seven days indicate a high probability of neurological remission, whereas increasing levels are associated with poor neurological outcomes.

Ketorolac

Ketorolac is a potent anti-inflammatory agent with three water-soluble crystals that inhibit cyclooxygenases COX-1 and COX-2 [51]. In all experimental studies of spinal cord ischemia, this drug is administered in the form of intrathecal infusion [51]. In one of the studies on ischemic S.C.I. rat model through intrathecal route when Ketorolac was administered 1 hour before induction of spinal cord ischemia, dosage 30 mg or 60 mg doses it was reported that intrathecal administration of 60 mg showed improved hind limb motor function and reduced neuronal cell death. [52]. This drug also reduces postoperative joint pain. Its intraarticular injection reduced the spinal activation of astrocytes at day one animal group, whereas the group which received ketorolac injection immediately after an injury did not have any effect [53].

Nanoparticle-based therapy

Nanoparticle-based approaches in S.C.I. have also played a significant role; in one of their study Cho., *et al.* 2010 In a guinea pig contusion model, showed that treatment by polyethene glycol coated silica nanoparticles helps in restoring the integrity of neuronal membrane leads to recovery of conduction through the S.C.I. lesion. Wang YT., *et al*. 2011 in one of their study on a rat S.C.I. model, demonstrated that local administration of gold nanoparticles conjugated with human NgR-Fc (hNgR-Fc) fusion protein vaccine promotes and improves the efficacy of repair in this rat model. Besides having their risks nowadays, nanoparticles based drug formulation is of great choice for treatment in the case of S.C.I. In their study Wilson SF., *et al*. 2019 demonstrated the most beneficial effect of Dexamethasone acetate (DA) micelles; it shows promising outcomes in replenishing hindlimb function, in minimizing deformity of glial cells, formation of cyst around the injured point, helps in axonal regeneration and reduce the loss of neurons in case of S.C.I. Rasti Boroojen and his co-workers have shown the effect of co-electrospinning of poly-ɛcaprolacton (P.C.L.)-containing dexamethasone sodium phosphate-albumin (DEXP-BSA)-loaded chitosan nanoparticles for the repair of S.C.I. In the later stage of S.C.I., extracellular uptake of glutamate, a neurotransmitter, by astrocytes is increased by polyethene glycol coupled with single-

walled carbon nanotubes. Chitosan, a polysaccharide polymer, is non-toxic, biodegradable, biocompatible, and accessible for surface modification due to it being preferred in biomedical sciences for wound healing, drug delivery and surgical adhesion. Chitosan nanoparticles are the best key player for functional recovery of motor and sensory neurons and are named 'membrane sealant' after neurotrauma or S.C.I. episodes. Another nanoparticle known as Roilipram has emerged as a promising candidate for targeting C.N.S. regeneration because of its ability to cross the blood-brain barrier. It is a phosphodiesterase (P.D.E.) IV inhibitor, known to uphold an apoptotic cell death, deplete both inflammatory cytokine and immune cell infiltration, increase cAMP via PDE IV inhibitor, reduce neuronal sensitivity, spare white matter space, and improve locomotor revival in SCI. a polymeric micelle nanoparticle PgP [poly(lactide-co-glycolide)-graft-polyethylenimine] acts as a carrier for rolipram in S.C.I. improvement developed by Mack., *et al.* 2018. It has been polymerized for combinational delivery of therapeutic nucleic acids and drugs for S.C.I. repair; it has a hydrophobic core and hydrophilic shell, which carries rolipram and small-interfering R.N.A. to the site of S.C.I. Zonisamide, an antiepileptic drug chemically known as 1,2-benzisoxazole-3-methanesulfonamide, is a clinically approved drug used worldwide; this drug has been used in treating psychiatric and other neurological impairments. Zonisamide-loaded MPEG-PLLA-PTMC [monomethyl poly (ethylene glycol)-poly (l-lactide)-poly (trimethylene carbonate)] nanomicelles in the S.C.I. model have targeted and recovered motor dysfunction which was induced in this model. other nanoparticles such as Self-assembled monomethoxy poly (ethylene glycol)-poly (d, l-lactic acid) diblock copolymer micelles have also shown promising results in reducing the inflammatory response in motor function recovery in spinal cord injured rats. In case of primary injury, these particles act as sealing agents. Fang C., *et al*. showed promising results of zonisamide-encapsulated gold nanoparticles in neuronal and axonal regeneration, thus contributing to S.C.I. recovery. In the case of S.C.I., for cellular survival, intracellular signalling, and axonal transport, microtubule stability is an urgent demand. A clinically accepted nano-drug known as Paclitaxel has a hydrophobic nature. It acts as a regulator for mitosis and microtubule formation. Due to its hydrophobic nature, it's easy to deliver it at the targeted injured site and has shown promising improvement of SCI. April Cox., *et al*. 2020 in one of his latest studies on rodents, showed the beneficial role of low dose estrogen delivery to the injury site to the spinal cord using an agarose gel patch embedded with estrogen-loaded nanoparticles and markedly found decreased post-injury lesion size, reactive gliosis, and glial scar formation. In contrast, an increase in the levels of glial cell-derived neurotrophic factors and axonal regeneration, vascular endothelial growth factor production also increases.

Thyrotropin Releasing Hormone (T.R.H.)

It is mainly secreted by neurons and is a small peptide found primarily on the brain. T.R.H. interacts with plasma membrane G-protein-coupled receptors; In humans, one T.R.H. receptor (TRH-R1) is detected, and in rodents, an extra (TRH-R2) is also present. The role of T.R.H. is well known in the hypothalamic-pituitary-thyroid axis; the primary function of T.R.H. is that it induces the synthesis and release of the thyroid-stimulating hormone produced by the adenohypophysis, which in turn stimulates the thyroid gland for the synthesis and secretion of thyroid hormones, i.e., thyroxine and triiodothyronine. Many studies have shown that apart from maintaining the function of the thyroid gland, it also helps in neurological function.

Improvement in motor and sensory function in case of both complete and incomplete injury after posttraumatic S.C.I. have been reported in many studies with the treatment of T.R.H. or its analogues. Acute S.C.I. subjects with both complete and incomplete injury when treated with T.R.H. (0.2 mg/kg intravenous bolus followed by 0.2 mg/kg/h infusion over six h) within 12 hrs of trauma. These subjects were examined at 24h, 72h, one week, one month and four months after injury. Their clinical examination, including motor and sensory testing and assigning a Sunnybrook score based upon the level of function, were performed. In the case of complete injury, no detectable treatment effects appeared. However, data were available from only six such patients at four months, whereas in the incomplete injury group, six treated and five placebo patients had 4-month evaluations. The placebo T.R.H. treated group has the highest sensory, motor, and Sunnybrook scores. T.R.H. has different properties such as antioxidant effects, membrane stabilising and anti-inflammatory effects, enhancing blood flow in the spinal cord.

Growth hormone (G.H.)

An endocrine hormone produced that regulates immunomodulation, metabolism, neural function

neuroregeneration produced mainly by somatotropes, is a single chain polypeptide, and is a chain of 191-amino acid. By the activation of signalling pathways, it directly binds to the G.H. receptor (G.H.R.) and exerts its effects now. In the spinal cord of many animals, growth hormone receptors have been described. In the rat model, when G.H. is administered, it binds specifically to G.H.R. present its spinal cord. Motor neurons of the spinal cord are sensitive to G.H.; it helps increase nuclear and cell body size in transgenic mice Hanci, Kuday, and Oguzoglu 1994 in one of their studies in rats, demonstrated that motor function dysfunction derived from spinal trauma had been attenuated by the treatment of G.H. Radiation exposure by radioactive isotope affect all types of neurons of the spinal cord, so G.H. helps in preventing the harmful effect of radiation, it was proved in of the study when with a systematic injection of Growth hormone rats model were treated then harmful effects of radiation in their spinal cord were prevented. In the recent study conducted by, in the case of a patient with incomplete spinal cord development having a deficiency in the activity of motor limbs when the patient was treated with G.H., he improved his motor function was reported.

Melatonin (M.T.)

In the dark phase of the circadian cycle, the pineal gland synthesised the melatonin hormone**.** This hormone exerts neuroprotective effects in an animal model of S.C.I. by mitigating the secondary injury by suppressing the oxidative stress and inhibiting cell apoptosis which is proved by recent studies on animal models. Another secondary inhibitor known as Melatonin, chemically called N-acetyl-5-methoxy tryptamine, is a methoxyindole derivative that acts as an antioxidant, the anti-inflammatory agent thought to be protective against secondary injury in the case of S.C.I. by scavenging away free oxygen radical It also helps activate cysteine protease and is associated with attenuation of Ca2+ influx. A recent study proves its neuroprotective role in the secondary pathophysiology of S.C.I. In one of their study, showed in S.C.I. rats that systemic administration of melatonin (10 mg/kg, i.p.) for a week helps in the decreased level of tissue injury as well as much improved bladder function was also reported in comparison to rats who were on vehicle treatment.AQP-1 expression in the spinal cord is reduced after S.C.I. injury when systematic subcutaneous administration of melatonin (10 mg/kg, once daily for 14 or 35 consecutive days, correlated with attenuation of behavioural and mechanical hypersensitivity, suggesting a possible role of AQP-1 in SCI-related pain. Many of these treatments have clinical potential but have yet to be translated into clinical practice. The concentration of Melatonin is very high in CSF. Studies on animal models have shown that Its deficiency delayed sensory and motor function recovery. Treatment with it accelerates motor function recovery, significantly inhibits neuronal apoptosis, and promotes neuronal repair.

Kai Gao., *et al.* 2020 in one of their study demonstrated the effect of Melatonin (M.T.) on spinal cord injury (S.C.I.). Their study showed that Melatonin promotes a lysosomal degradation process called neuronal autophagy, which inhibits apoptosis of nerve cells after S.C.I. Thus, the effect of the SIRT1/AMPK signalling pathway exerts its neuroprotective effect. They performed their experiments on rats and divided them into four treatment groups, i.e. SCI+MT+EX527 (SIRT1 inhibitor), SCI+MT, S.C.I., and sham operation groups; they observed that Melatonin started exerting its effect by promoting the recovery of motor functions in the hind limbs, as well as reduced the activity of cleaved-caspase-3, cleaved-caspase-9, and terminal deoxynucleotidyl transferase dUTP nick end labelling-positive neurons whereas in the anterior horn of spinal cord it increased the motor neurons survival after the 14th day after S.C.I. Their study also proves that Melatonin plays a role in the molecular mechanism by upregulating the expressions of Beclin-1, light chain-3B, SIRT1, p-AMPK proteins in the spinal cord tissue MT-treated rats on the 14th day after S.C.I. ZhijieYang., *et al.* 2020, in their latest study, explains that M.T. treatment after S.C.I. suppressed the accumulation and the proliferation of microglia and astrocytes and also downregulated the astrocytes. Quantitative PCR data showed that M.T. significantly down-regulated the proinflammatory markers iNOS, IL-1β and TNF-α expressions.

In contrast, it increased the expression of S.O.D., C.A.T. and GSH-Px contents and the decrease in M.D.A. content. In contrast, western blotting analysis showed that its treatment downregulated the expression of caspase-3, Bax and GFAP and upregulated the expression of Bcl-2. In one of the studies, demonstrated the influential role of Melatonin in the regulation of microcirculation disorders that plays a vital role in the normal function of spinal cord neurons, glial cells, and axons and in the progression of repair of the damaged blood spinal cord barrier (BSCB) In their study on S.C.I. mouse model they immediately administered Melatonin (5, 10, 25, 50, 100 mg/kg intraperitoneally following S.C.I., and

then compared with 48 h post-SCI group, they conclude that Melatonin treated group restrained microvessel loss; attenuated edema; protected the tight junction proteins, endothelial cells, and pericytes; decreased the number of cell apoptosis, and reduced MMP3/AQP4/HIF-1α/VEGF/VEGFR2 expression after S.C.I., and also reduced blood spinal cord barrier (BSCB) permeability in mice treated with Melatonin (50 mg/kg). In the secondary pathophysiology of S.C.I, this hormone is considered an antioxidant with a neuroprotective effect This hormone has an immense role in the spinal cord to protect the tissues. It acts as an antioxidant, has an anti-inflammatory effect, inhibits apoptosis, decreases oedema and helps repair the blood spinal cord barrier (BSCB).

Nimodipine

Nimodipine, an L type calcium channel blocker, showed a moderate result in the case of spasticity, one of the significant comorbidities of the spinal cord that hampers the quality of life and motor recovery. One of the studies performed by Maite Marcanton., *et al*. 2020 in a mouse model of chronic S.C.I. showed that nimodipine ultimately hampers the development of spasticity measured as increased muscle tone and spontaneous spasms. Nimodipine improves blood flow to the injured spinal cord in the laboratory setting. The abnormal muscle activities associated with spasticity remain inhibited even after the stoppage of the treatment. Constitutive and conditional silencing of the L-type calcium channel CaV1.3 in neuronal subtypes demonstrated that this channel-mediated the preventive effect of nimodipine on spasticity after S.C.I. This study identifies a treatment protocol and suggests targeting CaV1.3 could prevent spasticity after S.C.I.

Anti-nogo antibodies

Inhibitory molecules present in the myelin obstruct the regeneration of axon in the injured C.N.S. myelin-associated protein nogo a is the most potent inhibitor, so after nervous system injury, neutralization of nogo-a exhibits axonal regeneration in the injured tract and compensatory sprouting of uninjured tracts in animal studies. Anti nogo, an IgG antibody, has undergone a phase I safety trial in human subjects with acute sci as it also promotes axonal regeneration in C.N.S. injury. Zorner b., *et al*. 2010 in his study showed the potent role of human anti-human-nogo-a antibody in 52 patients with ASIA A to C cervical or thoracic injuries by administrating it within 4-14 days of injury for periods ranging from 24 h to 4 weeks, intrathecally into the lumbar spine, no adverse event of this antibody was reported, but efficacy trials are still ongoing (www.clinicaltrials.gov, nct00406016).loss of bladder control is a common problem after spinal cord injury. in acute spinal cord injury subjects, a human phase-i safety and tolerability trial with the intrathecal application of anti-nogo-a antibodies has been successfully concluded. In patients with acute tetraplegia for upper-limb motor recovery, a phase-two randomized European multicenter trial is still going on (https://nisci-2020.eu). bladder parameters will be monitored as part of the panel of secondary readouts in this trial. Data addressing potential beneficial effects of nogo-a suppression after sci in humans should become available soon. Klaus Kutcher., *et al.* 2018 demonstrated the role of an anti nogo antibody in humans. It assessed this antibody's pharmacokinetics, tolerability, and feasibility ati35 by administrating it intrathecally in 52 patients with acute, complete traumatic paraplegia and tetraplegia. Treatment started 4 to 60 days post-injury in sci subjects. There was no adverse event reported regarding ati355. In the case of paraplegic subjects, motor scores improved by 8 points, while in tetraplegic patients, mean total motor scores increased, with 3/19 gaining >10 points, and 1/19 27 points at week 48. In his review, Raihan Mohammed., *et al.* 2020 describes the beneficial use of anti-nogo antibodies in rats and primates in upregulating C.N.S. regeneration and improving sensory and motor function. In treatment with anti-nogo antibodies in the case of sci subjects, no adverse event has been reported, although genetic evidence for its efficacy is mixed. Rong-Rong Zhao., *et al.* 2013 in his study showed the effective response of combined treatment of anti-nogo-A and chondroitinase abc in treatment of sci subjects, anti nogo a therapy promotes the growth of the more significant number of axons having a diameter of > 3 μm and growth of finer axons with varicosities is promoted by treatment of ch abc, these results point to different functions of nogo-a and chondroitin sulfate proteoglycans in axonal regeneration. In contrast, the combination of both shows enhancing functional recovery. According to their protocol, the first administered anti-nogo-a or the control antibody anti-cyclosporin a by intrathecal infusion from the osmotic pump for two weeks in rats. After that, the pump was removed two weeks after the lesion. After one week of removing the pump, rats were given ch abc or the control enzyme penicillinase above and below the lesion through intraspinal injection. Subsequently, the rats received five intrathecal infusions of enzyme on alternate days for ten days; the rats in all groups started rehabilitation training one month after the lesion, seven days after the first enzyme injection.

Cell transplantation therapies

It is the most promising therapeutic therapy for S.C.I. treatment. Nowadays, various stem cells and mature somatic cells (neural stem cell, embryonic/pluripotent stem cells, mesenchymal/ hematopoietic neural cells, oligodendrocytes, astrocytes, Schwann cells, and olfactory ensheathing cells) stem cells are used as transplantation therapy to treat various stages of S.C.I.

Autologous mesenchymal stem cells (MSC)

Ling Ling Liau., *et al*. 2020, in their recent review, concluded the beneficial role of mesenchymal stem cell therapy in the case of sci, including novel biological therapies that can be applied along with MSC to enhance its efficacy. MSC's application in the injured spinal cord helps reduce secondary injury and protect the neural elements that survived the initial mechanical insult by suppressing the inflammation. M.S.C.s are also shown to differentiate into neuron-like cells and help rebuild damaged nerves tissues by stimulating neural stem cell proliferation. As M.S.C.s secrete paracrine factors that help protect the remaining axon and promote the regeneration of axons, it helps replace damaged cells by differentiating them into nerve cells. The secretion of VEGF, H.G.F., IGF-I, stanniocalcin-1, TGF-β, and GM-CSF promotes the survival of damaged neurons and oligodendrocytes M.S.C.s. Hur., *et al.* 2016 in one of their study demonstrated the role of an autologous adipose tissue-derived mesenchymal stem cell by intrathecal transplantation of it in 14 subjects with S.C.I.; there was improvement shown in sensory function in 10 subjects, motor function improvement was shown in 5 subjects whereas improved voluntary anal contraction was reported in 2 subjects with S.C.I. But in the M.R.I. examination, the lesion size remained unchanged. Bydon., *et al.* 2020 demonstrated the beneficial role of 100 million autologous ADSCs in treating S.C.I. subjects. ADSCs were delivered intrathecally in the subjects. There was improvement shown in ASIA sensory and motor score and quality of life as indicated by the higher Global Health Score. Jarocha., *et al*. 2015 reported that after S.C.I. injury in a 15 years old patient with complete injury A.I.S. (A) transplantation of BMNCs at ten weeks and then subsequent transplantation of autologous BMSCs at every 3-4 months for five times, and in 2 years follow up, A.I.S. grade improved from C to D (score increased from 112 to 231), and patient also received bladder filling sensation, control over the bladder, the anal sensation was restored, control over the body trunk, improvement in muscle strength of lower extremities from plegia to deep paresis and subject began to stand and walk with support. Sharma., *et al*. 2013 in his study of 56 subjects with chronic S.C.I. (mean duration of injury 64 months), transplanted BMNCs in them and found improvement in A.I.S. grade of 4 patients while improvement in Functional Independence Measure (F.I.M.) score was observed in 24 patients. Marcus Vinícius Pinheiro Mendonça., *et al*. 2014 conducted a non-control study in 14 subjects of both genders of traumatic injury of fewer than six months of thoracic or lumbar level. Bone marrow-derived mesenchymal stem cell was directly injected into the lesion following laminectomy and durotomy after culturing and characterizing it by flow cytometry, cell differentiation assays and G-band karyotyping. In all the subjects, improvement in tactile sensitivity was observed, gain in motor function in the lower limb, especially in the hip flexor, was observed in 8 subjects, sacral sparing was presented in 7 subjects and improved (A.I.S.) grades to B or C - incomplete injury. In contrast, improvement in urologic function was observed in 9 subjects, while in 1 subject, improvement in somatosensory evoked potentials (SSEP) was observed. Zhilai Zhou., *et al*. 2020, in their study on a mouse model, demonstrated the role of adipose-derived mesenchymal stem cell (ADSC) transplantation on the inflammatory reaction after spinal cord injury (S.C.I.) and the potential mechanism mediated by Jagged1/Notch signalling pathway suppression. Zengjie Fan., *et al*. 2020 Design fabricated pre vascularized nerve conduits (P.N.C.) based on the pre vascularized stem cell sheet. They demonstrated its repair effect in transected S.C.I. rats; they found that for promoting better healing of S.C.I., improving the condition of ischemia and hypoxia and inhibiting glial scar formation P.N.C. is potential alternative material biomaterials and the best effective solution for S.C.I. rehabilitation. Many studies have shown that stem cells revealed their therapeutic role by secreting factors into their surroundings via a paracrine mechanism, like extracellular vesicles, one of the emerging extracellular vesicles having diameter are 40-150 nm. They have attracted increasing attention in regenerative medicine called exosomes. They act as the communication medium between cells by carrying different proteins, lipids, R.N.A. (mRNA, noncoding R.N.A., etc.) and other biological macromolecules and regulating the gene expression or protein synthesis of target cells; they influence the physiological function of the targeted cell. Studies also showed that when human adipose mesenchymal stem cells (hADSCs)-derived exosomes were injected in and around the wounds in rodents' skin, they significantly promoted angiogenesis

at the lesion site and accelerated wound healing. Besides that, exogenous stem cell exosomes also facilitate tissue regeneration and repair at the injured site when directly administered. Rong Y., *et al.* 2019 demonstrated that neural stem cell-derived exosomes (NSCs-Exos) after traumatic spinal cord injury reduce neuroinflammation and cell apoptosis by mediating the activation of autophagy. Dong Zhong., *et al*. 2020 demonstrated in their study that after traumatic spinal cord injury, the weakly physical strength of spinal cord microvascular endothelial cells (SCMECs) is one of the leading causes of augmentation of the spinal cord. Therefore, to promote recovery after spinal cord injury, it is crucial to improve the plasticity and regeneration of SCMECs, So they focused on the influence of exosomes derived from neural stem cells. So they extracted primary SCMECs from the spinal cord tissue of C57 mice and neural stem cells from 14 days pregnant C57 mouse after that, exosomes were isolated from N.S.C.s conditioned medium. After that co-incubated with the SCMECs *in vitro*, the result showed that NSCs-Exos could enhance the angiogenic activities of SCMECs and were highly enriched in VEGF-A; they accelerated the microvascular regeneration, reduced the spinal cord cavity and improved Basso mouse scale scores in spinal cord injury mice. Jun Gu., *et al*. 2020 in his latest study in both the vivo model and a series of *in vitro* experiments, demonstrated that the smallest membrane-bound nanovesicles called exosomes derived from bone marrow mesenchymal stem cells (BMSC-Exos) could reduce neuronal apoptosis by enhancing the expression of LC3IIB and Beclin-1 autophagy-related proteins and permitting the formation of autophagosomes. Marked declination in the level of expression of proapoptotic protein cleaved caspase-3. In contrast, upregulation in the anti-apoptotic protein Bcl-2 was observed after BMSC-Exos treatment, thus promoting the potential efficacy of functional behaviour in S.C.I. rats. In one of the recent studies, demonstrated the role of human adipose-derived stem cell (hADSC) infusion on the functional recovery of the impaired hindlimb and urinary continence after spinal cord contusion in rats. They divided the rats into two groups (B and C) of injured spinal cords and transplanted hADSCs in them 7 and 14 days after injury. In addition, group C receives methylprednisolone sodium succinate (MPSS) after 3hrs of injury, whereas the control group neither receives corticoids nor stem cells. After transplantation, motor performance and voiding performance were evaluated daily for 90 days. There was significant improvement observed in urinary continence of animals from groups B (66.6%) and C (66.6%), and partial recovery in the motor function of both groups were observed. B (23.8%) C (19%). He concluded in his study that transplantation of hADSCs with or without MPSS equally contributes to the improvement of motor function and voiding in case of spinal cord injury. Olfactory Ensheathing Cells or olfactory ensheathing glia cells found both centrally and peripherally along the olfactory nerve. In S.C.I. rats, O.E.C. grafts yielded promising regeneration, remyelination, and functional locomotor improvements in the corticospinal axon. In one of the studies, the potential role of bone marrow stem cell transplantation in 9 subjects with chronic S.C.I. with complete injury has given a promising result with improved locomotor and sensory function after three weeks follow up. The beneficial role of autologous bone marrow mononuclear cells in the case of 56 chronic cervical spines brings improved functional recovery and betterment in the quality of the subject of life when administered intrathecally, proved by one of the clinical trials at Neurogen Brain and Spine Institute, Mumbai (NCT02009124). Studies were conducted to compare the efficacy of BM-MSCs and UC-MSCs in treating S.C.I. survival rate of UC-MSCs is higher in comparison to BM-MSC. However, both cells help suppress neuropathic pain and improve motor recovery after S.C.I. (at T6-T8 levels). Transplantation timing of any stem cell also plays a crucial role in the assessment of the recovery of the injured spinal cord; it was proved by one of the studies on mouse model on post-transplantation of hNSCs in female rodents (T-10 level) at acute (immediate after the introduction of S.C.I.), subacute (7 days after S.C.I.), and chronic (28 days after S.C.I.) After assessment through Basso, Beattie, and Bresnahan (B.B.B.) locomotor rating scores, no significant differences were seen in their recovery phase. In contrast, the subacute group shows maximum improvement compared to the chronic phase group when determined from the time of cell injection.

Acidic fibroblast growth factor

Growth factors are responsible for modulating the survival of damaged neurons after spinal cord injury by promoting axonal regeneration, sprouting of neurons, and blocking inhibitory molecules. Two types of G.F.s such as essential fibroblast growth factor (bFGF) and nerve growth factor (NGF), are mainly responsible in the central nervous system for promoting axonal regeneration, angiogenesis and neurogenesis. Xiaoli Hu., *et al.* 2020 in one of his recent studies that S.C.I. recovery is a multifactorial

process, so multiple growth factors participation helps in better recovery by tissue regeneration, as only direct administration of single G.F.s rapidly degrade and dilute at the injured sites. So for promoting early and better recovery, controlled delivery of multiple growth factors (G.F. s) to lesion areas is now becoming a fascinating strategy for repairing S.C.I. So they developed G.F.s -a based delivery system known as GFs-HP, through self -assembly mode it contains fibroblast growth factor (bFGF), nerve growth factor (NGF) and heparin-poloxamer (H.P.) hydrogel. It is a kind of thermosensitive 3D porous structure hydrogel used to load many G.F.s and was suitable for orthotopic administration *in vivo*. After a single injection of GFs-HP into the lesioned spinal cord, complete recovery in motor function, axonal regeneration, improved neuronal survival, and reactive astrogliosis suppression. Their study also revealed that neuroprotective and neuro-regenerative effects of GFs-HP are because of activating the phosphatidylinositol three kinase and protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signalling pathways. In one of their recent review, explain that growth factors play a vital role in improving transplantation in animal models, as neural precursor cells (N.P.C.s) plays a potential role in improving neural regeneration after S.C.I. but unfortunately in the injured spinal cord the survival and differentiation of transplanted N.P.C.s is meagre. Their study assessed the effect of growth factors in their reduced number and in different concentrations to increase proliferation and differentiation of N.P.C.s *in vitro*. In immunosuppressed Wistar rats, model of cervical clip contusion S.C.I. at the C6 level, and transplanted N.P.C. and in addition intrathecally administered growth factors for ten days after injury (EGF, bFGF, and PDGF-AA), after eight weeks of S.C.I. they observed surviving N.P.C.s in the injured animals that efficiently differentiated into oligodendrocytes and oligodendrocytic precursors, and in addition improvement in "Average Speed" in the Catwalk gait analysis, and in "Stride length" were seen after eight weeks of S.C.I.

No effects on the B.B.B. score were observed, and no regeneration was observed in descending tracts and posttraumatic myelination. Still, posttraumatic inflammation and apoptosis were suppressed after N.P.C. transplantation and G.F. administration. One of the most promising growth factors used for S.C.I. therapy is BDNF, whose effect in increasing motor function shortly after injury was observed in small animal models; however, the statistical significance of this effect disappears at later follow-ups. It acts as the best neuroprotective agent because it helps hire oligodendrocytes and promotes myelination of damaged and growing axons. But in its further follow-up, there was a drop in improvement over control, which suggests that BDNF alone is not accurate in spur axonal regeneration. But other studies showed that BDNF and fibroblast graft showed better results in inducing axonal regeneration. A recent study conducted by Saikrishna Kandalam., *et al.* 2020 in one of their recent study on the S.C.I. mouse model showed that dental stem cells from the apical papilla (SCAP)with pharmacologically active microcarriers (P.A.M.s) releasing brain-derived neurotrophic factor (BDNF) would help in promoting locomotory function in rats by neuroprotection and immunomodulation. They prepared BDNF-PAMs by emulsifying poly(L-lactide-co-glycolide), and nano precipitated BDNF and then coated it with fibronectin; after that, SCAP was seeded on it, and its expression of neuronal and immunomodulatory factors was evaluated *in vitro*. A mouse model demonstrated that providing Injection of SCAP BDNF-PAMs at the lesion site help in improving their B.B.B. score, helps in the reduction of inducible nitric oxide synthase, and increases the expression of βIII tubulin, GAP43, and 5-HT.

Hepatocyte growth factor (H.G.F.)

Mesenchymal cells are responsible for the secretion of HGF. The secretion of H.G.F. is increased after S.C.I. to promote the migration of mesenchymal cells at the injury site. Studies have proved that H.G.F. helps reduce glial scar and promotes functional recovery.

Functional electrical stimulation (F.E.S.)

F.E.S. is used for rehabilitation settings dates back to the 1960s. In his recent review, Cesar MarquezChin et al. 2020 concluded that it's the best electrical technique applied to paralysed person's muscles to make them contract in a sequence to perform tasks such as grasping any object or holding a toothbrush, standing and walking. Nicholas J. Batty., *et al*. 2020 demonstrated that neuronal cAMP levels decline after traumatic injury, which has been associated with the limited ability of neurons to regenerate, so electrical stimulation is the best way to increase neuronal cAMP post-injury. To stimulate a long-lasting axonal growth stimulation program single session of electrical stimulation is sufficient. In their study, they promoted the growth and plasticity of the corticospinal

tract with cortical electrical stimulation immediately after its spinal injury in rats; rehabilitative motor training was also given to them for translating plasticity into functional recovery, they had given a rehabilitative exercise to all rats (i.e., with or without electrical stimulation). Their findings reveal that cortical electrical stimulation improves recovery of forelimb function earlier in comparison to recovery in unstimulated animals. Patients having hemiplegia as a result of stroke is drop foot, a condition of decreased ability to perform ankle flexion and extension in the affected lower limb, as a result of which patient is unable to walk because the foot cannot clear the ground, so correction of this defect using electrical stimulation is the simplest and oldest neuroprosthesis for walking. In one of their recent review, describes that the significant number of antibiotics such as macrolides, minocycline, β-lactams, and dapsone, exerts protective effect such as anti-inflammatory and neuroprotective in the case of S.C.I. by improving its sequels and complications by targeting signalling pathways such as reducing inflammatory microglial activity, promoting autophagy, inhibiting neuronal apoptosis, and modulating the SCI-related mitochondrial dysfunction.

Cerebrospinal Fluid Drainage

CSF drainage helps to reduce spinal cord perfusion and reduce ischemia by relieving pressure, similar to external ventricular drainage (E.V.D.) for elevated intracranial pressure (I.C.P). This technique is mainly implemented for routine treatment of thoracoabdominal aortic aneurysm surgery despite the treatment of acute traumatic SCI. One study demonstrated that M.A.P. elevation with CSF drainage maximizes spinal cord blood flow after S.C.I. in an animal model. However, the study was underpowered. In contrast, no significant adverse events were recorded in subjects in one of the phase I study trials in 2009 on CSF drainage in humans (n = 22). No differences in ASIA scores between cases and controls at six months were noted.

Nutritional supplementation

In one of his meta-analyses on the role of nutritional supplementation of Vit C and E on spinal cord injury animal model and concluded that daily supplementation of both nutraceuticals either alone or in combination significantly helps in improving motor function in animals suffering from S.C.I., in addition, studies proved that supplementation of vitamin C is only effective when administered intraperitoneally, whereas concomitant supplementation of both vitamins does not show better efficacy than treatment of both vitamins alone. DUE TO ITS ANTIOXIDATIVE PROPERTIES, Vitamin C or ascorbic acid protects other organs, including the spinal cord, in an animal model. Wang., *et al.* 2015 in their study demonstrated that supplementation of vitamin C is effective against renal damage induced due to S.C.I. by inhibiting proinflammatory cytokines and nuclear factor-kappa. In another study conducted by Chao Chen., *et al*. 2020 on nutritional supplementation of combined effects of taurine and Ascorbic acid in S.C.I. induced rats. They divided the rats into four groups: sham, control, 100 mg/kg of taurine, 100 mg/kg of ascorbic acid, and 100 mg/kg of taurine + 100 mg/kg of ascorbic acid, and continued his treatment daily for 45 consecutive days and reported that the combined treatment of taurine and ascorbic acid decreased the activity of caspase-3 by 33.7% and p53 by 44% respectively, as well as activity of pro-NGF, mRNA expression of interleukin-6 (IL-6), cyclooxygenase-2, tumour necrosis factor-alpha (TNF-α), and inducible nitric oxide synthase (iNOS as compared to the individual treatment of both taurines as well as vit C. Whereas changed antioxidant markers were recovered and induced lipid peroxidation comes to its normal level after the combined treatment of both. In his study on adult Sprague-Dawley rats, Kathia Cordero., *et al.* 2018 demonstrated when fed with a normal diet. In another group, when fed with a dietary regiment supplemented with vitamin E (51 IU/g) for eight weeks after that, the rats were exposed to contusive S.C.I. or sham operation; they reported that rats that were administered with vit E enriched diet showed accelerated bladder recovery, as well as improved locomotory function compared to rats that were fed with normal diets, as well as several oligodendrocytes in the ventral horns, were also increased. In one of the latest studies, K Pritchett., *et al*. 2019 demonstrated the beneficial role of Vit D supplementation in athletes with spinal cord injury because athletes with S.C.I. have insufficient status of 25 (O.H.) vitamin D (25(O.H.) D) that is associated with decreased muscle strength. In their study, Thirty-four members (age: 33 ± 15 years, weight: 69.6 ± 28.2 kg, and height: 170.2 ± 25.4 cm) of the U.S. and Canadian Paralympic program participated in the study. After pre and post supplementation of Vit D (50,000 IU/week) for eight weeks to subjects deficient in 25(O.H.) D, and to subjects showing the insufficient status of 25(O.H.), D received 35,000 IU/week for four weeks, after that, both groups received a maintenance dose of

15,000 IU/week. They received supplementation of Vitamin D totally for 12- to 16-week.It was observed that 26% of athletes had sufficient 25(O.H.)D concentrations pre supplementation. In contrast, about 91% had sufficient concentrations post supplementation, whereas handgrip strength is improved post supplementation in about 62% of participants, whereas no change in 20-m wheelchair sprint performance was observed. Evaluated that patients suffering from S.C.I. are Vit D deficient and mostly higher body mass index, lower A.D.L. functional independence, and poor LTPA (leisure-time physical activity). So their study demonstrated that Low Vit D in S.C.I. is an indicator symbol of poor physical function. In the latest study, demonstrated the role of folic acid administration that actively suppressed MMP-2 expression by methylating the D.N.A. sequence that encodes for the MMP-2 protein. As we know, Matrix metalloproteinase (M.M.P.) is greatly responsible for early disruption of the blood spinal cord barrier, leading to myelin sheath disruption, promoting macrophages infiltration, and giving rise to neuropathy pain. So they report that F.A. administration (80 µg/kg body weight) intraperitoneally (I.P.) reduced cSCI-induced N.P. by inhibiting MMP-9 in the proposed mid-phase cSCI. This study discovers a new phase of cSCI that is the mid-phase. It is concluded from their study that F.A. treatment exhibits a significant effect on MMP-9 and MMP-2 expression, and modulation of their expression is time and location dependent. MMP-9 by F.A. mostly occurs in the early phase of injury, whereas MMP-2 modulation by F.A. occurs mostly in the latest phase of S.C.I. Demonstrated the anti-inflammatory role of injectable hydrogel containing tauroursodeoxycholic acid (TUDCA) in a spinal cord injury (S.C.I.) mouse model. By immersing the synthesized hydrogel in TUDCA solution for at least 1 hour. T.C. gel was injected in induced mechanical S.C.I. rats; it was observed that motor functions and lesions were significantly improved in the T.C. gel group in comparison to the saline group. In another study, in his recent study on folic acid and topiramate supplementation, demonstrates that ectopic discharge that is originated from injured sites and dorsal root ganglion after peripheral nerve injury sometimes contributes to neuropathic pain; Voltage-dependent Na channels are responsible for the ectopic discharge, activity of voltage-gated sodium channel is blocked topiramate (TOP) by blocking type of glutamate receptor, i.e. amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptor and the activity of folic acid (F.A.) in neurotransmitter synthesis reactions, both F.A. and TOP acts as an anti-apoptotic agent by phosphorylated-Akt (p-Akt) signalling activation and anti-inflammatory effects at the injury site. They investigated their effect (F.A. and TOP) on rats with sciatic nerve injury by treating them with these drugs once daily for six months; they concluded that both have similar effects on myelin sheath formation and axon outgrowth. Whereas F.A. Non pharmacological approaches best promoted positive effects on axonal regeneration by increasing the number of axons, including natural vitamins that are easy to administer and cost-effective. They directly attack the generation of R.O.S. and R.N.S. that further retard LPO and cellular damage. Vitamins are natural antioxidants; Vitamin A promotes the release of IL-1β, IL-6, and TNFα and thus improves neuroprotection. By reducing the level of R.O.S., R.N.S., LPO, glutathione activity, and peroxidases, Vit E accelerates functional recovery in S.C.I. subjects. Selenium also plays an important role in S.C.I. due to its antioxidative activity. It also promotes neuroprotective activity against oxidative stress accompanying S.C.I. Enzymes Glutathione peroxidase (GPx) and thioredoxin reductase (TrRx) also contains selenium. Therefore, it helps prevent oxidative stress associated with R.O.S. production. Diets rich in ω-3 acids also play an important role in promoting neuroplasticity and regeneration of nerve cells by changing the concentration of proteins participating in it, i.e., protein kinase B (Akt) and cAMP-response element-binding (CREB) protein, proves by collecting tissues of S.C.I. rats. After S.C.I. there is gradual bone loss, leading to increased morbidity and mortality of fragile fractures, so many studies prove that bisphosphonate is the principal medication used for osteoporosis in S.C.I. subjects. In one meta-analysis, demonstrate that bisphosphonate therapy, when administered early after S.C.I., may prevent bone loss in the lumbar spine and hip region and has a high safety effect. Their metanalysis included Six R.C.T.s, in which 147 subjects met the inclusion criteria. It was observed that B.P.s administration finickily prevents bone loss in the femoral neck, total hip and trochanter at the 6- and 12-month follow-up points and increase the BMD of the lumbar spine at the 12-month follow-up time point, however on the clear effect of this drug is shown on serum PINP or serum calcium level at the 12-month follow-up time point. Taurine is the unique non-essential amino acid that has betrayed much attention. The heart and brain are the only two organs that produce their taurine in a minimal quantity. Mohammad Mehdi Ommati., *et al*. 2019 showed the potential effect of taurine on a mouse model of manganism against Mn neurotoxicity when manganese exposed mice were treated with different doses of taurine (50, 100, and 500 mg/kg,

i.e.,) alleviated Mn-induced locomotor deficit. Daniel Sobrino., *et al.* 2020 demonstrated in their study that role of taurine helps in the modulation of axonal regeneration following a complete spinal cord injury using lampreys as an animal model; their result offers a novel pathway to make an effort to promote axon regeneration after nervous system injuries in mammalian models). In the case of a mouse model of spinal cord injury S.C.I., it was reported that when taurine (25, 80, 250, and 800 mg/kg, i.e.,) treatment was given, it ameliorated motor disturbance and pathological anomalies, the taurine treatment also helps in the reduction in the level of IL-6 and myeloperoxidase in a dose-dependent manner, and its treatment helps in the decline -mediated cyclooxygenase-2 and phosphorylated signal transducer and activator of transcription three expressions. Taurine treatment reduced neutrophil accumulation exclusively in the subarachnoid spaces and induced secondary degenerative deviations in the gray matter.

Scaffolds

At MSc transplantation, injectable hydrogels and scaffolds act as the matrix to accelerate cell engraftment and survival. Natural, synthetic or combined materials are used to prepare injectable hydrogels and scaffolds. Using the rat S.C.I. model, it has been demonstrated that M.S.C.s seeded in the fibrin scaffold up to 10 weeks scaffold showed good viability upon transplantation. Scaffold helps in retaining cell survival at the lesion site and supports the cell's survival; it promotes angiogenesis and neurogenesis and enhances the cell's capacity to suppress fibrosis and inflammation by modulating the action of cells function.

Furthermore, the scaffold can inhibit glial scar formation, subside inflammation, stimulate angiogenesis, and promote neurogenesis. Zhao., *et al.* 2017 in one of his studies, conclude that scaffold treatment can regulate the wound microenvironment to assist in spinal cord regeneration. In his study on eight patients with chronic complete S.C.I., they were treated with a collagen scaffold called NeuroRegen, along with umbilical cord blood-derived M.S.C.s (UCBMSCs) and found that it helps in stimulating sensation level as well as elevate the motor evoked potentials (M.E.P.s) responsive area even though there was no change in ASIA grade.

Spinal cord stimulation

Concerning spinal cord stimulation, in patients suffering from S.C.I. and chronic pain, epidural spinal stimulation has well been tested in these subjects. Many studies prove that epidural stimulation of the spinal cord showed improved ability to make lower extremity voluntary movements in subjects with SCI ASIA A and B. Lu DC., *et al.* 2016 in one of his case studies, showed the effect of epidural spinal stimulation once a day in respect of the upper body. A promising result was obtained in patients' handgrip strength and motor strength of the upper extremities. Another safe and non-invasive technique for spinal cord stimulation is transcutaneous stimulation which involves the placement of electrodes onto the skin surface of S.C.I. subjects. In this method, surgical placement of electrodes onto the spinal cord's dorsal surface.

Activity-dependent plasticity

This method has been recently employed to achieve substantial improvements in motor function; for long term improvement in motor function that can be offered to S.C.I. subjects, neurorehabilitation is the most current treatment strategy for this case. This technique involves high-intensity training and electrical neuromodulation that has shown a promising improvement in neuronal connection and circuits within the spinal cord by working collusively at least in a subpopulation of patients; this technique helps in motor recovery after SCI.

Brain stimulation for S.C.I

It is one of the currently employed methods. The two main approaches used to augment the neuronal plasticity between the spinal cord and the brain in individuals with S.C.I. are transcranial direct current stimulation and transcranial magnetic stimulation. In the case of complete S.C.I., the motor function seems to improve by transcranial direct current stimulation. It's a non-invasive method used to deliver direct current using scalp electrodes. Transcranial magnetic stimulation is also a non-invasive approach that transfers magnetic waves to the brain, and in the case of subjects with tetraplegia, improved hand function has been shown. Transcranial magnetic stimulation has improved handgrip strength and delicate motor tasks. And its positive impact has been noticed on the patient's walking speed as proved by one of the trials. This deep brain stimulation has been tested in animal studies; its potential in treating patients with S.C.I. still needs to be elucidated with clinical trials and further research.

Tendon and nerve transfers

Due to loss of motor endplates after 12 to 18 months in the

case of S.C.I., musculature undergoes irreversible atrophy. Nerve transfer can occur within 18 months to achieve the best outcomes. Compared to tendons, it takes longer to achieve functional results (3 to 12 months) but provide greater fine motor control, which can continue to improve many years after surgery. In contrast, tendon transfer shows a sooner result than neurotization and is also not time-limited but is contraindicated by spasticity and requires extended immobilization after surgery.

Beneficial effects of tendon transfer have been shown in juvenile S.C.I. patients; after surgery, the assessment of hand function betray significant improvements in terms of pinch force, which improved considerably during the first year of treatment. Unilateral and bilateral functions facilitated the patient's independence in hand functions concerning eating, brushing teeth, writing, and applying toothpaste confirmed through the analysis: functional Independence Measure (F.I.M.) and the Common Object Test (C.O.T.).

Apart from neurological consequences, the most challenging and distressful conditions in men with S.C.I. are erectile dysfunction, ejaculatory dysfunction and abnormal semen quality. After this severe condition, S.C.I. subjects pose the biggest challenge of their biological fatherhood due to ejaculatory dysfunction and poor semen parameters. To overcome this strategic condition, two main techniques, viz Penile vibratory stimulation (P.V.S.), and electroejaculation are first-line modalities for ejaculation. Surgical sperm retrieval (S.S.R.), sperm obtained by this mentioned technique, is used for various fertility treatments for couples with spinal cord injured men. One of the recent studies by Nikita Naredi., *et al*. 2021 in his prospective observational study, demonstrated that when partners of 12 men with S.C.I. underwent assisted reproduction after retrieving sperms through various treatment modalities, they found that Sperm ejaculation was more through the P.V.S. technique(7) in comparison to S.S.R. (4). Men who underwent P.V.S. resulted in a higher pregnancy rate of 57.14% than couples who underwent S.S.R. 75%, with an overall pregnancy rate of 58.33% through the in-vitro fertilization cycle. Yuyong Chen., *et al.* 2021 in one of their study showed the therapeutic effect of miR-26amodified MSC-derived exosomes (Exos-26a) following S.C.I. in the animal model and observed its molecular mechanism that it plays an essential role in axonal regeneration as well as help in improving neurogenesis and attenuate glial scarring through activating PTEN/AKT/mTOR signalling cascades.

Conclusion

It has been investigated that the advancement in neuroprotective pharmacology, stem cell technologies, nanoparticles-based approaches and neuromodulation is used for the treatment of S.C.I. We investigated that most of the studies have been performed on an experimental animal model, more trials and research needs to establish their efficacy in human. Among different techniques, it has been concluded that nutritional supplementation is easy to administer and cost-effective and safest mode, there are two studies already ongoing on nutritional supplementation in the department of orthopaedic surgery KGMU, on traumatic spinal cord injury and positive effects against bedsores and improvements in their A.I.S. grading scale has been noticed. Recent advances in accurate, timely, and practical classification methods of acute spinal cord injury will assist in the development of novel treatment approaches for both acute and chronic injury alike.

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