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Pharmacological Treatment of Acute Spinal Cord Injuries in the Light of Recent Developments

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ABSTRACT

Spinal injuries represent a significant public health issue with both individual and societal implications due to its potential to result in long-term or permanent disability and death. Today, notwithstanding the comprehensive elucidation of the mechanism of injury in its all aspects and breakthroughs in early diagnosis techniques and treatment, spinal injuries still retain their devastating nature. Although many agents hypothesized to possess neuroprotective and neuroregenerative properties have been demonstrated to be effective in the experiments, research involving human subjects is still in progress, offering promising developments. Methylprednisolone at a high dose is the most extensively investigated therapeutic for acute spinal injuries. Despite significant controversy, it remains a viable treatment option. It is anticipated that combining stem cell transplantation with multiple pharmacological agents will yield more favorable outcomes.

Keywords: Spinal injuries, Pharmacological agents, Stem cell transplantation

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Introduction

Spinal injuries are complex traumas that mostly occur resulting from mechanisms of blunt trauma, involving damages including fractures and dislocations of bone structures in the vertebral column, as well as lesions such as tearing and rupture of the soft tissue surrounding the column and/or damages to the spinal canal or the spinal cord within it (Wyndaele & Wyndaele, 2006). Spinal injuries represent a significant public health issue with both individual and societal implications due to its potential to result in permanent disability and death. Today, although the mechanism of injury has been elucidated in all aspects and breakthroughs in early diagnosis techniques and treatment, spinal injuries still retain their devastating nature. Given the vital role of the vertebral column and spinal cord, such injuries are likely to cause physical, psychological, social and economic problems, thereby significantly impacting both the injured individuals and their families and social surroundings (Devivo, 2012). Hence, it is crucial to initiate the treatment for spinal injuries as early stage as possible and to ensure the optimal management and treatment for patients (Wyndaele & Wyndaele, 2006; Karsy, & Hawryluk 2019).

Mechanism of Injury and Physiopathology

For decades, it has been understood that spinal cord trauma involves both primary and secondary injury mechanisms of biological processes. This mechanism, which was first described by Allen in 1911, recognises that primary injury is an inevitable result of energy transfer and the initial traumatic impact. Direct mechanisms including compression, contusion, laceration, as well as sudden increase in tension in the spinal vascular structure can give rise to this condition (Kwon et al., 2004; Fehlings et al., 2017). Such injury has the potential to result in a complete or partial anatomical lesion in the spinal cord. Secondary injury encompasses several mechanisms that initiate immediately after trauma and extend over weeks. In addition to the systemic response of the entire body to trauma, secondary injuries are observed as a result of the local, biochemical, histopathological, ion-mediated and/or oxidative cellular responses, and alterations in the spinal cord. These mechanisms are often complicated and interconnected and may result in delayed or secondary death of neuronal and glial support cells (Can et al., 2021; Yılmaz & Kaptanoğlu, 2015). Although it is theoretically inferred that pharmacological agents have the potential to target and restore these trauma-induced cascades, limited progress has been achieved so far in this regard (Yılmaz et al., 2015; Allan et al., 2015).

Initial Management of Acute Spinal Injuries

Until clinically and radiologically proven otherwise, it is acted upon the presumption that there is a spinal injury in cases of multiple and high-energy traumas. It is imperative to evaluate and transfer such patient by ensuring immobilization of the spine immediately following the incident. Also, during the primary evaluation process in emergency departments, care should be taken to ensure spine immobilization during interventions including examination and imaging as well as advanced airway provision (Fehlings et al., 2017). Clinical conditions such as hypotension and bradycardia (spinal shock findings) resulting from loss of control over vagal tone, and paralysis of respiratory muscles, should be identified and controlled early during a systematic physical examination that encompasses all systems. Considering that spinal shock symptoms may be confused with hemorrhagic shock in a traumatised patient, a differential diagnosis should be established and appropriate shock treatment should be initiated. Prompt initiation of fluid replacement and vasopressors should be initiated in the case of hemodynamic deterioration (O'Toole et al., 2019; Hadley et al. 2002). Once the patient should be stabilised in terms of respiration, circulation and neurology, and placed within a safety perimeter with continuous monitoring, they should be sent for imaging (Fehlings et al., 2017; Allan et al., 2015).

Conventional and Current Medical Treatment Approaches for Spinal Injuries

Currently, ongoing trials on the treatment for traumatic spinal cord injuries aim to prevent and restore secondary damage at the cellular level, as well as to mitigate the systemic secondary effects of trauma, including hypotension and hypoxia. The primary medical treatments applied for these purposes can be categorized under the headings of "neuroprotective therapies" preventing the progression of cord damage, including vasoactive medications to improve spinal perfusion, and "neuroregenerative therapies" aiming to restrore neuronal regeneration and myelination. The definitive treatment for these injuries will be achieved through advances in regenerative therapies, like cell transplantation, that seek to restore the damaged spinal cord.

1. Neuroprotective Therapies in Acute Spinal Injuries

Nowadays, there are ongoing trials for neuroprotective therapies aimed at treating numerous neurological

pathologies. The pharmacological agents used for this purpose are mostly well-established drugs that have been proven to be effective. It is also widely recognized that optimizing the timing of administration is crucial for achieving the highest level of effectiveness. While some agents are currently undergoing trial phase, the findings from both animal and human research show promising outcomes for the treatment of spinal trauma.

a- Regulation of haemodynamics and vasoactive pharmacotherapy: One could anticipate hypovolemia and hypovolemic shock as outcomes of trauma. Nevertheless, hypotension and hypoperfusion may manifest in cases of spinal injuries where sympathetic innervation loss occurs resulting from spinal damage in the absence of hypovolemia. This condition, which is particularly common in injuries above the level of the 6th thoracic vertebra, is referred to as spinal or neurogenic shock. The clinical differentiation between this shock and classical hypovolemic shock is based on the presence of bradycardia rather than tachycardia. The detrimental impact of hypotension on the damaged spinal cord, and preventing hypotension and maintaining blood pressure at targeted values reduces mortality and improves neurological outcomes are well-documented (Can et al., 2021). Guidelines emphasize the importance of maintaining the Mean Arterial Pressure (MAP) value high as avoiding hypotension (Hadley et al., 2013; Cozzens et al., 2013). Treating the hypoperfusion caused by spinal shock, will require more than just therapies that fill the vascular bed used in hypovolemic shock, often vasopressors will be needed to be used to increase blood pressure. The most preferred pharmacological agents for this purpose are Dopamine (1-10 mg/kg/min) and Norepinephrine (1-20 mg/min), which induce vasoconstriction with α- and β-agonist activities and increase cardiac activity. Dobutamine, Epinephrine and Phenylephrine can also be used (Streijger, et al., 2017; Ryken et al., 2013). A number of studies on how cord perfusion can be increased in spinal injuries have obtained data suggesting that the drainage of Cerebrospinal Fluid (CSF) increases perfusion. Further, data suggest that when CSF drainage and elevation of Mean Arterial Pressure (MAP) are performed together, intrathecal pressure increases by 5.45 mmHg, and this increase positively affects spinal cord perfusion by 24% (Streijger, et al., 2017; Jutzeler et.al., 2023; Can et al., 2021).

b- Corticosteroid Therapy: There are numerous studies on the use of corticosteroids in spinal trauma. The earliest views on this subject suggested that steroids were beneficial due their anti-inflammatory activity. Subsequent studies have shown that methylprednisolone has a free-radical scavenging effect. As mentioned earlier, disruption of membrane integrity by free radicals is one of the most important causes of secondary tissue damage. It has been claimed that high-dose of methylprednisolone increase medullary blood flow in the early stage of spinal cord injury, thereby improving perfusion, reducing excitotoxicity and neuronal phagocytosis mediated by immune mediators. Dexamethasone and other steroids have not shown any efficacy (Coutinho et al., 2011). The results of the International Acute Spinal Cord Injury Study-I (NASCIS-I), comparing the efficacy of low-dose methylprednisolone with high-dose methylprednisolone, emphasised that high-dose methylprednisolone did not result in significant neurological recovery but was closely associated with adverse outcomes such as wound infection, pulmonary embolism, gastrointestinal hemorrhage, sepsis and high mortality risk (Bracken et al., 1985). Similarly, in NASCIS-II, which compared high dose methylprednisolone and Naloxone (Opiad antagonist) with a placebo in the first 12 hours following trauma, no significant difference was found in neurological outcomes between the study groups. However, when the results of the subgroup consisting of patients treated with methylprednisolone within the first eight hours were examined, which was included in the study methodology, it was observed that although motor power recovery was quite significant in patients in this group, while complication rates such as wound site infection and pulmonary embolism were lower (Bracken et al., 1990). The latest study on this subject, NASCIS III, compared high-dose methylprednisolone with an antioxidant 21- aminosteroid (trilazad mesylate) within the first eight hours of trauma. This study, which also compared 24-hour infusions of both agents, found no difference between the triazilad mesylate and methylprednisolone groups. However, it was claimed that patients receiving a bolus dose of methylprednisolone after spinal injury also undergo a 48-hour infusion, their neurological outcomes at one-year was favourable. After the NASCIS III study, a 24-hour methylprednisolone infusion was recommended in patients receiving treatment within the first three hours after trauma, and a 48-hour methylprednisolone infusion was recommended in patients receiving treatment within three to eight hours (Bracken et al., 1997). Many researchers have conducted studies adopting the protocols of NASCIS II and III and reported that these protocols, especially those of NASCIS III, did not result in a significant increase in neurological recovery and led to many severe side effects, including secondary deaths. A revision was made to the methylprednisolone recommendations in the guidelines issued by the American Association of Neurological Surgeons/Central Nervous System (AANS/CNS) approximately 15 years after the last NASCIS

protocol. It was underscored that the use of methylprednisolone in acute spinal injury lacked approval from the Food and Drug Administration (FDA), that there were no supporting findings of classes 1 and 2 for the clinical benefits of this administration, and that high-dose corticosteroid administration was associated with multiple complications, including death, as indicated by findings of classes 1, 2 and 3. Consequently, it was highlighted that it is more appropriate to administer high-dose methylprednisolone for 48 hours rather than 24 hours, and treatment should commence within the first eight hours rather than eight hours following the injury (Hurlbert et al., 2015). In contrast, a large meta-analysis conducted in 2020 stated that methylprednisolone treatment within the first 8 hours did not yield a statistically significant short- or long-term improvement in overall motor or neurological scores of patients compared with steroid-free controls. Furthermore, it induced an increased risk of pneumonia and hyperglycaemia compared to controls, indicating that its routine use should be carefully considered. The use of steroids for acute spinal cord injuries and if used, the strategy to be followed, remains controversial today.

c- Minocycline: Minocycline is actually a synthetic, antibiotic of tetracycline class that has been tested in oncological and degenerative diseases of the nervous system, Alzheimer's disease and stroke. In recent years, it has also been used in acute spinal injuries. It plays a neuroprotective role through its multifaceted mechanism of action with its anti- inflammatory, antioxidant and apoptosis inhibitory properties. Many preclinical studies have shown that it improves motor functions, reduces lesion size and provides axonal protection (Festoff et al., 2006; Wells et al., 2003). A Phase II study on minocycline emphasises that although it is not very effective in lumbar spinal injuries, there are positive data on motor recovery in cervical spinal injuries (Casha et al., 2012).

d- Ganglioside GM-1: A glycolipid molecule located in the membranes of mammalian central nervous system cells has been indicated to exhibit potential neuroprotective effects in acute spinal injuries by experimental studies. In addition to its anti-apoptotic and excitotoxicity-inhibiting effects, it also accelerates axonal regeneration (Can et al., 2021). Although the results from initial studies on the use of this molecule for acute spinal injuries are promising, similar results have not yet been obtained from more comprehensive, multicentre and long-term patient follow-up studies. Therefore, it is not included in the new guidelines (Cozzens et al., 2013; Jutzeler et al., 2023).

e- Riluzole: This agent, a sodium channel blocker and an anticonvulsant of the benzothiol class, has been used for the treatment of Amyotrophic Lateral Sclerosis since the discovery of its neuroprotective effects in the 1990's. It inhibits glutamate excretion presynaptically and mediates glutamate transfer in synaptic intervals. It inhibits guanylyl cyclase cascade by voltage-dependent sodium channel blockade and limits the excitotoxic effects of glutamic acid released by cellular death. It is the only drug approved for neuroprotective activity. There are experimental studies and completed phase trials on the use of Riluzole in acute spinal injuries (Can et al., 2017).

f- Amantadine: Although primarily an antiviral medication, this agent is also used in the treatment of Parkinson's disease. It is believed to be effective by inhibiting the reuptake of dopamine in the synaptic cleft and increasing dopamine release from vesicles, thus showing high dopaminergic activity. Additionally, it acts as a sympathomimetic. The survival-enhancing and neuroprotective properties of this agent are thought to be exerted through dopaminergic, sympathomimetic, and N-methyl-D-aspartate receptor antagonism (Yılmaz & Kaptanoğlu, 2015).

g- Glyburide: Glyburide, also known as glibenclamide, is used as an antidiabetic agent. It is a nonspecific cation channel blocker and regulator of sulfonylurea receptor-1. In addition to stimulating insulin release, it is claimed to reduce hemorrhagic necrosis, oedema and inflammation through its effect in the microvascular area, thus leading to successful results in experimental modelling of hemorrhagic stroke and traumatic brain injury. It has been found that decreases in bleeding up to 24 hours following injury or bleeding, and the lesion begins to shrink within six weeks (Kurland et al., 2013; Popovich et al., 2012).

h- Magnesium (Mg): This element, which is a factor in the healthy functioning of many systems in the human body, has been found useful as a neuroprotective agent in many central nervous system diseases, including cerebral palsy. Mg, which is an N-methyl- D-aspartate receptor antagonist, reduces inflammation by inhibiting cytokines and reduces free radical levels. It prevents glutamate-dependent excitotoxicity. In two experimental studies on the efficacy of Mg on traumatic spinal injury, Mg was administered in polyethylene glycol, which facilitates blood brain barrier passage and improves biodistribution, and was found to be more effective than methylprednisolone, especially in the return of motor functions (Kwon et al., 2009; Lee et al., 2010). However, the effectiveness of Mg in spinal injuries has not yet been proven in human studies (Temkin et al., 2007). Phase II human studies on Mg are still

ongoing today (Karsy et al., 2019).

i- Granulocyte Colony Stimulating Factor (G-CSF): A glycoprotein produced endogenously which induces the production and release of granulocyte and stem cells into circulation by stimulating the bone marrow. It is claimed to promote functional recovery and provide neuroprotection in many degenerative nervous system diseases. It has been emphasised that non-hematopoietic functions such as protection of myelin structure, stimulation of angiogenesis, and TNF-□ and IL-1 suppression also contribute to this effect (Karsy et al., 2019). However, in two separate studies conducted on patient groups with spinal injury, although ASIA scores improved in the follow-up of patients treated with autologous stem cells and Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), no improvement in neurological functions or reduction in toxicity reduction were detected after treatment (Park et al., 2005; Yoon et al., 2007).

j- Naloxone: This agent, an opiate antagonist, is thought to be effective in acute spinal injuries as it decreases the activity of nitric oxide synthetase and superoxide dismutase. In NASCIS-II, it was shown that there was no difference between methylprednisolone and placebo treatment groups in terms of motor recovery. (Bracken et al., 1990).

k- Erythropoietin: It is known that this molecule exerts its non-hematopoietic glioprotective and neuroprotective effects by reducing medullary cavitation, cell infiltration and apoptosis. Its derivatives produced via recombinant technology that do not induce erythropoiesis, yet to be tested in human trials, are considered promising for spinal traumas (Alibai et al., 2015). Furthermore, new studies have been conducted to investigate the combination of erythropoietin with more established pharmacotherapies for the treatment of traumatic spinal injury (Ganjeifar et.al., 2021).

l- Rolipram: While clinical trials have yet to establish its effectiveness, experimental evidence suggests that Rolipram can improve motor and sensory functions in traumatic spinal injuries in rats. The anti-inflammatory effects of Rolipram, a phosphodiesterase inhibitor, are thought to be responsible for these outcomes (Nikulina et al., 2004).

m- Nimodipine: A L-type calcium channel blocker that inhibits apoptotic enzymes and reduces the release of glutamate at synapses. It is known to regulate microvascular circulation, thereby increasing spinal cord blood flow. Although the first study on nimodipine was conducted in 1996, its efficacy on neurological recovery has not been proven superior to placebo (Fehlings et al., 2017).

n- Tirilazad mesylate: A synthetic 21-Amino-steroid molecule specially produced to inhibit peroxidation of lipids in neuronal membranes, was suggested that it has comparable efficacy to methylprednisolone in the NASCIS-III study. However, the lack of placebo-controlled studies and its similarity to methylprednisolone in terms of complications have reduced the availability of this drug (Bracken et al., 1997; Boyalı et al., 2020).

o- Mannitol: It is known that mannitol should be initiated for anti-edema treatment in spinal injuries at early stage where there are no contraindications without any reason (Huang et al., 2019).

p- Induced Hypothermia: In recent years, there has been considerable interest in the application of local or systemic induction of hypothermia for both the treatment of injuries and the care of comatose patients, due to its ability to reduce oxygen consumption by decreasing metabolic rate. Although there is not abundant supporting evidence, direct cooling of the spinal tissue intraoperatively has been used to treat spinal cord injuries for decades. Induced hypothermia was once more a subject of discussion in 2007, when it was nearly abandoned, after it was administered to an injured professional footballer and the patient regained sufficient motor function to walk within a very short time. Whether the early neurological recovery in this case was due to hypothermia is open to speculation. This favourable outcome may be due to early decompression and spontaneous neurological recovery, which have been observed in some cases (Kwon et al., 2008; Dietrich et al., 2011). There are no universally acknowledged indications or contraindications for induced hypothermic therapy. It is advisable to administrate it when there are no inhibitory factors associated with the patient and when adequate medical facilities are available (Martirosyan et al., 2017; Boyalı et al., 2020). Experimental research emphasizes that optimal temperature range for systemic hypothermia is 32-340C, which is considered moderate hypothermia (Ahmad et al., 2014). Local hypothermia can be administered via irrigating the epidural and/or subdural space with cold water at 6°C, inducing hypothermia (Dididze et al.,2013; Hansebout et al.,2014).

2. Neuroregenerative Therapies in Acute Spinal Injuries

Strategies targeting neural regeneration for treatment

of spinal injuries aim not to stop secondary injury, but rather to activate and/or strengthen the organism's own repair mechanisms. The main goal of these treatment strategies is to overcome factors that impede recovery such as inhibitory molecule signalling, scarring, loss of structural framework, cavitation. The correct timing of these treatment plans may vary depending on the patient, the general medical condition of the patient, as well as factors such as which strategy is more appropriate in which period. For example, some treatment plans are more beneficial in the acute phase immediately after the injury, while others are more beneficial in the subacute or chronic phase. The other concomitant therapies and the timing of these therapies are also of special importance (Ahuja et. al., 2016; Boyalı et al., 2020). Some of the most well-known neuroregenerative treatments are given below.

A- Myelin-linked inhibitor targeting therapy:

a. Anti-Nogo-A Antibodies: Based on the idea that Nogo-A, a proteinaceous building block of myelin, has a significant reducing effect on neuronal growth (Chen et al., 2000), experimental studies carried out by intrathecal injection of selective Nogo-A antibodies to some experimental animals, revealed that this antibody increased the restructuring and regeneration of axons in the damaged medulla spinal cord. Phase I and phase II clinical trials on this subject are ongoing (Zorner et al., 2010; Boyalı et al., 2020).

b. VX-210 (Cethrin®): A modified form of C3 transferase derived from C. botulinum with promising developments in its use for traumatic spinal injuries. The paste form of this therapeutic is known by the trade name Cethrin and can be administered directly to the dura mater during the operation. It is effective in axonal growth and functional recovery and has the ability to prevent apoptosis. It exerts this effect by inactivating Rho and Rho-Associated Kinase, which hinder neuronal growth (Forgione et al., 2014). Phase I/IIa trials on this topic have shown its effectiveness on motor recovery in injuries of the cervical and thoracic regions, more prominently in thoracic injuries. There was also an increase in sensory recovery in patients with thoracic injuries (Fehlings et al., 2011).

B- Treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

Many types of this group of drugs, which are frequently used in clinical practice, contribute to axonal regeneration by inhibiting the Rho pathway. Experimental studies have shown that NSAIDs may target cyclooxygenases in spinal injuries and improve motor functions (Xing et al., 2011; Sharp et al., 2013).

C- Fibroblast growth factor (Fibroblast growth factor; FGF):

FGFs, which are potent mitogens that stimulate cell proliferation and regeneration of stem cells, are actually a collection of 22 proteins that signal with different tyrosine receptor kinases together with their own receptors. By increasing the proliferation of stem cells, it has been predicted that they may be included in treatment combinations in the treatment of traumatic spinal injury. In an experimental study, it was claimed that it may also be effective by promoting angiogenesis after spinal injuries (De Laporte et al., 2011). There is an FGF analogue with proven neuroprotective and neuroregenerative properties, but phase II trials have not been completed and no results regarding its effects in humans have been reported (Shi et al., 2014). Phase I trials for another FGF-impregnated biomedical device are undergoing (Karsy et al.2017).

D- Hepatocyte Growth Factor (HGF):

This molecule, known to act as a neurotrophic factor by stimulating angiogenesis, has been reported to be promising as it has been shown to protect fibres of the corticospinal tract in primate models of cervical spinal injuries and to be supportive motor functions of the upper extremities (Kitamura et al., 2011). Phase I/II studies of human-derived HGF obtained with recombinant technology are ongoing (Boyalı et al., 2020).

E- Chondroitinase ABC:

Another method that is thought to provide neuroregeneration in spinal injuries is the targeting of the existing glial scar tissue. Glial scar is a formation that impedes neuronal growth and the penetration of regeneration therapies. An experimental animal study demonstrated that chondroitinase ABC, an enzyme produced by bacteria, cleaves the glucose chains and proteoglycans in the glial scar and thus supports functional recovery (Bradbury et al., 2002). For the future medical treatment of spinal injuries, it has been suggested that the combination of this molecule with Anti-Nogo-A will have highly effective in providing therapeutic benefits (Zhao et al., 2013).

3. Cell Transplantation Approaches in Acute Spinal Injuries

Recent advancements in stem cell transplantation have

sparked new hypothesis regarding its potential therapeutic applications in acute spinal injuries. Prior to the current understanding of stem cells, it was postulated that central nervous system tissue lacked the capacity of regeneration. Nevertheless, this contention has been refuted by the demonstration that multipotent neuronal stem cells can differentiate into neurons, astrocytes and oligodendrocytes under favourable conditions (Barnabé-Heider et al., 2018). The strategy of stem cell transplantation in acute spinal injuries includes certain goals such as replacement of damaged neurons, stimulation the release of various trophic factors, and regulation of the microenvironment (Antonic et al., 2013). To date, however, only a handful of small studies have examined the efficacy of stem cell transplantation in patients with spinal trauma, furthermore, the results are highly variable (Donelly et al., 2012; Boyalı et al., 2020). Concerns regarding the risk of neoplasms arising from transplanted stem cells and limited functional recovery have not been ruled out in the studies conducted to date. Continuation of the treatment strategy with adjuvant therapeutics and combinations with one or more neurotrophic agents mentioned above are thought to improve the results (Boyalı et al., 2020; Taylor et al., 2006).

4. Neuropathic Pain Management in Acute Spinal Injuries

Gabapentin (GBP) and Pregabalin (PGB): Secondary clinical conditions following spinal injuries include depression, anxiety, sleep disorders and neuropathic pain, which are difficult to resolve. More than half of the cases following this form of injury exhibit neuropathic pain (Gustorff et al, 2008). It may cause the patient's daily activities, routine and quality of life to be disrupted, thereby exacerbating preexisting conditions. While anticonvulsants have been used for the treatment of this condition for years, today, GBP and PGB are the first-line treatment options for neuropathic pain caused by spinal injuries. PGB, a new generation of gabapentinoids with a comparable mechanism of action to GPB, is the only drug approved for this indication by the US Food and Drug Administration. For years, both GBP and PGB have been safety used as therapeutics for clinical conditions such as postherpetic neuralgia and diabetic peripheral neuropathy (Teasell et al., 2010).

5. Management of Complications in Acute Spinal Injuries

a- Management of respiratory complications: Clinical pathologies of the respiratory system such as recurrent pneumonia, atelectasis, and pleural effusion are common following spinal injuries. Pulmonary problems are particularly common in cases of upper or mid-level cervical spinal injuries, as damage to the phrenic nerve exit area. Symptoms such as dyspnoea, chest pain and cough may be present. Death due to pulmonary pathologies is common in cervical spinal injury. Treatment may involve frequent and deep breathing exercises, respiratory physiotherapy, and bronchial clearance if necessary. Mechanical ventilation is started if necessary with close blood gas monitoring. The patient should be followed up in appropriate wards or intensive care unit according to the patient's clinic status. Pharmacotherapy may include the use of agent-specific antibiotics, symptomatic treatment and bronchodilators (Hadley et al., 2002; Boyalı et al., 2020).

b- Management of cardiovascular complications: In the short period following cervical spinal injuries, activation of the sympathetic system is suppressed and parasympathetic dominance begins. Symptoms such as hypotension, bradycardic rhythm and increased secretions are common. We have mentioned that especially cervical and upper thoracic injuries can cause "neurogenic shock" and its management. In the absence of neurogenic shock, it will be appropriate to monitor the fluid balance to correct hypotension and to replace it when necessary. A vasopressor agent may be necessary to ensure adequate perfusion. Atropine (0.5-1 mg Iv push) can be used to correct symptomatic bradycardia (Karsy et al., 2019).

c- Management and prophylaxis of deep vein thrombosis (DVT): Patients with spinal injury are predisposed to DVT due to prolonged immobilisation. Clinically symptomatic DVT has been reported to be as high as 17%, and the incidence of DVT detected by imaging has been reported to be almost 80%. Consequently, the incidence of thromboembolic events such as pulmonary embolism is also increased. The risk is further increased in cases where spinal injuries are accompanied by pelvic and lower extremity fractures. Regular use of compression stockings and limb exercise are routinely recommended for the management of DVT risk in spinal injuries. Unless there are absolute contraindications, one of the prophylaxis regimens of low dose subcutaneous Heparin (5000 U) twice daily or Low Molecular Weight Heparin (Enoxaparin) 20-40 mg/day should be initiated. The primary goal should be to mobilise the patient as soon as the vertebral column is stabilized (Karsy et al., 2019; Can et al., 2021)

d- Management of gastroentrological complications and nutrition: Partial ileus may develop in most cases with spinal injury. In addition, caution should be exercised in such a patient, as the acute abdomen may progress without

clear clinical features. During the acute phase of the injury, a gastric tube should be inserted via nasal or oral route in order to prevent gastric distension and potential perforation. Sucralfate and proton pump inhibitors or H2 receptor antagonists can be employed for prophylaxis of acute gastroesophageal reflux disease and peptic ulcer which may result from both the stress caused by trauma and high dose steroid use. In patients with spinal injury, inadequate nutrition may lead to problems related to immunity and wound healing by causing catabolic energy supply. However, oral/enteral nutrition may not always be possible, particularly during the acute phase. In these cases, intravenous hyperalimentation rich in lipids should be initiated early. Enteral nutrition via jejunostomy or gastrostomy may be considered in indicated cases (Fehlings et al., 2017; Can et al, 2021).

e- Management of urological complications: Persistent urinary tract infections appear to be the most prevalent urological complication among patients with acute spinal injury. To prevent these infections from leading to hydronephrosis and renal failure, it is crucial to perform periodic bladder irrigation and urinary catheter use, as well as replacing the catheter at least once a week. In case of urinary infection, it should be treated with agent-specific antibiotherapy (Landi, 2003).

f- Management of hyponatraemia: The drop in serum sodium concentration that occurs approximately 6-9 days following trauma, reaches lowest level between 9-17 days, and typically rebounds to normal levels within 24-36 days. Despite the fact that clinical trials have documented varying frequencies ranging from 45% to 100%, it is evident that this is a commonly encountered complication. The main causes include high levels of cervical injury, concomitant infective conditions, intensive care conditions and ventilator use, and certain medications, especially diuretics. If the underlying cause is the Syndrome of Inappropriate Antidiuretic Hormone (SIADH), refined carbamide can be used, while Cerebral Salt Wasting Syndrome (CSWS), fludrocortisone can be used (Ohbe et al., 2019, Chavasiri et al., 2022).

g- Management of musculoskeletal and cutaneous complications: The most common skin and soft tissue issue encountered is pressure sores. Preventing the development of pressure ulcers is the most effective treatment strategy. This primarily entails ensuring the patient is properly positioned and repositioned frequently as well as using specialized manufactured pressure-relieving mattresses. Massaging the skin with moisturizing lotions can be beneficial. The skin should be carefully examined frequently and even superficial ulcers should be treated by covering with sterile occlusive dressings. Severe pressure sores may require surgical debridement. Common musculoskeletal problems such as contusions and spasticity can be minimised with physiotherapy (Eli et al., 2017).

Future Prospects in Medical Treatment of Spinal Injuries

Future prospects for the treatment of these types of injuries lie in more preventive or restorative strategies for secondary injury mechanisms. In the light of the studies conducted so far, it can be asserted that promising developments for favourable outcomes lie in combinations of numerous pharmacotherapies related to neuroprotective, neuroregenerative and stem cell transplantation therapies, whether their efficacy has been proven or they are still under investigation. Although the abundance of these combination options complicates the situation, the multiplicity of possibilities raises expectations for the future (Yılmaz et al., 2015; Fehlins et al., 2017; Can et al., 2021; Karsy et al., 2019).

Conclusion

Spinal injuries remains a formidable subject for scientific investigations owing to their complex pathophysiology, heterogeneity of patients and mechanism of injury, and serious comorbid conditions. Despite all the achievements, complete neurological recovery has not yet been achieved. The insights and expertise gained from the results of studies conducted thus far will assist in the development of future clinical management strategies. Expectations are high that more encouraging results can be achieved with multiple pharmacological agents accompanying stem cell transplantation.

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