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SOFT PACKING INTERVENTIONS IN SPINAL CORD INJURY: CURRENT INSIGHTS AND FUTURE DIRECTIONS

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Abstract: INTRODUTION: Spinal cord injury (SCI) involves a complex interplay of primary and secondary injury mechanisms, resulting in sensory, motor, and autonomic dysfunction. Understanding these processes is critical for developing effective interventions to mitigate tissue damage and promote neural repair. Strategies such as soft packing interventions and pharmacological approaches offer promise for enhancing recovery. Rehabilitation, preventive measures, and addressing epidemiological disparities are essential components in improving outcomes and reducing the global burden of SCI. Collaborative efforts across disciplines are crucial for advancing SCI management and enhancing the lives of affected individuals. **OBJETIVE:** To analyze and describe the main aspects of interventions in SCI in the last years. **METHODS:** This is a narrative review, in which the main aspects of SCI in recent years were analyzed using studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases. **RESULTS AND DISCUSSION:** SCI initiates a complex cascade of pathophysiological events involving primary and secondary injury mechanisms, leading to sensory, motor, and autonomic dysfunction. Primary injury, occurring immediately upon impact, involves physical disruption of spinal cord tissue, while secondary mechanisms, unfolding over hours to weeks, exacerbate neurological deterioration. Strategies targeting scar formation modulation and neuroregeneration hold promise for enhancing functional recovery post-SCI. Pharmacological interventions aim to attenuate secondary injury mechanisms and promote neural repair, while non-pharmacological approaches complement rehabilitation efforts, optimizing outcomes. Understanding SCI's epidemiology, prevention strategies, and management is crucial for reducing its global burden and improving the lives of affected individuals. **CONCLUSION**: SCI is a multifaceted condition marked by primary and secondary injury mechanisms leading to severe sensory, motor, and autonomic deficits. Therapeutic strategies such as soft packing interventions hold promise for modulating scar formation and promoting axonal regeneration.
Keywords: Spinal Cord Injury; Neurology; Traumatology.

INTRODUCTION

Spinal cord trauma, commonly referred to as spinal cord injury (SCI), is a devastating condition characterized by damage to the spinal cord resulting in a range of sensory, motor, and autonomic dysfunctions[1]. Such injuries often occur due to traumatic events like vehicle accidents, falls, sports injuries, or violence. The severity of SCI varies depending on the location and extent of damage along the spinal cord. Injuries can be classified as complete, where there is a total loss of sensation and motor function below the level of injury, or incomplete, where some degree of sensory or motor function remains[2]. The pathophysiology of SCI involves primary and secondary injury mechanisms[1]. Primary injury occurs at the moment of trauma, leading to immediate disruption of neural tissue, while secondary injury encompasses a cascade of processes including inflammation, oxidative stress, excitotoxicity, and apoptosis, which exacerbate tissue damage and contribute to functional impairment over time[2]. Understanding the complex mechanisms underlying SCI is crucial for developing effective therapeutic strategies aimed at minimizing secondary damage and promoting neural regeneration to improve outcomes for individuals with spinal cord trauma[1,2].

Advancements in medical technology and

rehabilitation strategies have significantly improved the management and outcomes of individuals with spinal cord trauma[3]. Early interventions such as immobilization, surgical decompression, and pharmacological agents targeting secondary injury mechanisms aim to reduce further damage to the spinal cord and improve neurological function4. Rehabilitation plays a crucial role in the recovery process by enhancing physical function, promoting independence, and optimizing quality of life for individuals with SCI[3]. Techniques such as physical therapy, occupational therapy, and assistive devices facilitate neuroplasticity and functional recovery by promoting adaptive changes in the central nervous system[3]. Moreover, emerging therapeutic approaches including stem cell transplantation, neuroprotective agents, and electrical stimulation hold promise for enhancing neural repair and regeneration following SCI[4]. Collaborative efforts between clinicians, researchers, and individuals with SCI are essential for advancing our understanding of spinal cord trauma and translating scientific discoveries into clinical practice to improve the lives of affected individuals[3,4].

SCI encompasses a spectrum of pathological processes initiated by mechanical injury to the spinal cord, resulting in immediate damage and subsequent secondary injury mechanisms[2]. The primary injury occurs at the moment of impact and involves mechanical disruption of neural tissue, including axonal shearing, contusion, or laceration[5]. The extent and severity of primary injury depend on various factors such as the force and direction of trauma, as well as the anatomical location along the spinal cord[5]. Following the primary insult, secondary injury mechanisms are activated, leading to further tissue damage and functional deficits[2,5]. These secondary processes include inflammation, excitotoxicity, oxidative stress, apoptosis, and disruption of the blood-spinal cord barrier. Inflammatory responses involve the release of cytokines, chemokines, and immune cells, exacerbating tissue damage and contributing to neuronal death[5]. Excitotoxicity, mediated by excessive release of excitatory neurotransmitters such as glutamate, leads to calcium influx, mitochondrial dysfunction, and neuronal degeneration[2]. Oxidative stress further amplifies tissue damage through the generation of reactive oxygen species, causing lipid peroxidation, protein oxidation, and DNA damage. Apoptosis, or programmed cell death, contributes to neuronal loss and glial scar formation, impeding axonal regeneration and functional recovery[2,5]. Understanding the complex interplay of these secondary injury mechanisms is crucial for developing targeted therapeutic interventions aimed at mitigating tissue damage and promoting neural repair following spinal cord trauma[5].

Furthermore, disruption of the blood-spinal cord barrier (BSCB) following spinal cord trauma plays a pivotal role in secondary injury mechanisms and the progression of neurological deficits[6]. The BSCB, analogous to the blood-brain barrier, regulates the exchange of nutrients, ions, and cells between the systemic circulation and the spinal cord parenchyma, maintaining homeostasis and protecting the central nervous system from harmful substances[7]. Traumatic injury to the spinal cord compromises the integrity of the BSCB, leading to increased vascular permeability, extravasation of blood components, and infiltration of immune cells into the injured tissue[5]. This breakdown of the BSCB exacerbates secondary injury processes by facilitating the entry of pro-inflammatory mediators, cytotoxic molecules, and immune cells into the spinal cord, amplifying tissue damage and neuroinflammation[6,7]. Moreover, disruption of the BSCB disrupts

the microenvironment necessary for neuronal survival, axonal regeneration, and remyelination, further impeding functional recovery following spinal cord trauma. Strategies aimed at preserving BSCB integrity and restoring barrier function represent potential therapeutic targets for attenuating secondary injury mechanisms and improving outcomes in individuals with SCI[6,7].

SCI is a significant public health concern, with a considerable impact on individuals, families, and healthcare systems worldwide[8]. Epidemiological studies provide valuable insights into the incidence, prevalence, and demographic characteristics of SCI, aiding in the development of preventive strategies and resource allocation[9]. The global incidence of SCI varies across regions and populations, with estimates ranging from 10.4 to 83 cases per million population per year[8,9]. Males are disproportionately affected, accounting for approximately 80% of all SCI cases, likely attributed to higher rates of risky behaviors and participation in activities associated with traumatic injury, such as sports and motor vehicle accidents[9]. The leading causes of SCI include motor vehicle accidents, falls, violence, and sports-related injuries, with the distribution of etiological factors varying by age, sex, and geographical location. Advancements in medical care and rehabilitation have contributed to improvements in survival rates following SCI, leading to a growing population of individuals living with long-term disabilities[7]. Comprehensive epidemiological data are essential for understanding the burden of SCI, informing policy decisions, and implementing targeted interventions to prevent injuries and enhance outcomes for affected individuals[7,9].

Furthermore, the epidemiology of SCI demonstrates notable variations in risk factors and outcomes among different populations and age groups[9,10]. While traumatic SCI predominantly affects young adults, particularly males aged 16 to 30 years, non-traumatic SCI is more prevalent in older individuals, often associated with degenerative conditions such as spinal stenosis, disc herniation, or vascular disorders[9,10]. Geographic disparities in SCI incidence reflect differences in socio-economic status, healthcare infrastructure, and environmental risk factors. For instance, low- and middle-income countries exhibit higher rates of SCI due to limited access to preventive measures, inadequate road safety regulations, and higher rates of violence[9]. Conversely, developed countries with better infrastructure and healthcare systems may experience a higher prevalence of non-traumatic SCI related to age-related degenerative conditions. Additionally, disparities in access to rehabilitation services and assistive technologies contribute to variations in functional outcomes and quality of life among individuals with SCI[8,11]. Addressing these disparities requires a comprehensive approach encompassing injury prevention strategies, improved access to healthcare services, and socioeconomic interventions to mitigate the burden of SCI and promote health equity on a global scale[10,11].

OBJETIVE

To analyze and describe the main aspects of interventions in SCI in the last years.

SPECIFIC OBJECTIVES

1. To review the current state of soft packing interventions in the management of SCI, including their effectiveness, limitations, and challenges.
2. To examine the biomechanical principles underlying soft packing interventions and their impact on spinal cord mechanics and tissue regeneration.
3. To explore recent advancements in soft packing materials, techniques, and

technologies for SCI treatment and rehabilitation.

4. To discuss the potential mechanisms of action of soft packing interventions, such as neuroprotection, tissue remodeling, and axonal regeneration.

METHODS

This is a narrative review, in which the main aspects of SCI in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Spinal Cord Injury:" AND "Traumatology" AND "Neurology" in the last 10 years. As it is a narrative review, this study does not have any risks. Only studies in English and were selected.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

RESULTS AND DISCUSSION

SCI entails a complex cascade of pathophysiological events that occur following traumatic insult to the spinal cord, resulting in varying degrees of sensory, motor, and autonomic dysfunction[2]. The pathophysiology of SCI can be broadly categorized into primary and secondary injury mechanisms[12]. Primary injury occurs immediately upon impact and involves physical disruption of the spinal cord tissue, including contusion, compression, laceration, or transection. This initial insult disrupts the blood-spinal cord barrier, leading to hemorrhage, edema, and ischemia, which exacerbate tissue damage and impair neuronal function[10]. Secondary injury mechanisms, which unfold over hours to weeks following the primary insult, further contribute to neurological deterioration and functional deficits[12]. These secondary processes encompass inflammation, excitotoxicity, oxidative stress, apoptosis, and disruption of the blood-spinal cord barrier. Inflammatory responses involve the release of pro-inflammatory cytokines, chemokines, and immune cells, amplifying tissue damage and perpetuating neuroinflammation[12]. Excitotoxicity, mediated by excessive release of neurotransmitters such as glutamate, results in calcium influx, mitochondrial dysfunction, and neuronal death[2]. Oxidative stress further exacerbates tissue damage through the generation of reactive oxygen species, causing lipid peroxidation and protein oxidation. Apoptosis, or programmed cell death, contributes to neuronal loss and glial scar formation, impeding axonal regeneration and functional recovery[2]. Understanding the intricate interplay of these primary and secondary injury mechanisms is crucial for developing targeted therapeutic interventions aimed at mitigating tissue damage and promoting neural repair following SCI[2,12].

Following SCI, the formation of fibrotic and astroglial scars represents a complex and dynamic process with significant implications for tissue repair and functional recovery[13]. Fibrotic scar formation involves the deposition of extracellular matrix (ECM) components, predominantly collagen, by fibroblasts and infiltrating immune cells, creating a dense network of scar tissue at the injury site[14]. This fibrotic scar acts as a physical barrier, inhibiting axonal regeneration and impeding neuronal repair[14]. Concurrently, reactive astrocytes undergo a process known as astrogliosis, characterized by hypertrophy, proliferation, and upregulation of intermediate filament proteins such as glial fibrillary acidic protein (GFAP)[13]. The astroglial scar, composed of densely packed astrocytic processes and associated ECM molecules, encapsulates the lesion site, and modulates the inflammatory response[14]. While the astroglial scar initially

serves a protective role by limiting the spread of inflammation and preserving tissue integrity, it also creates a microenvironment rich in inhibitory molecules, such as chondroitin sulfate proteoglycans (CSPGs), which impede axonal growth and regeneration. Strategies aimed at modulating scar formation and promoting a permissive environment for axonal regeneration hold promise for enhancing functional recovery following SCI[13,14].

Understanding the mechanisms underlying spinal cord recovery pathways is crucial for developing effective therapeutic strategies to promote neural repair and functional recovery following injury[15]. In response to SCI, a multifaceted cascade of cellular and molecular events is initiated, encompassing both intrinsic and extrinsic factors[15]. Intrinsic mechanisms involve the activation of endogenous neural stem cells, neuronal plasticity, and axonal sprouting, which contribute to spontaneous regeneration and rewiring of neural circuits[16]. Additionally, remyelination by oligodendrocyte precursor cells (OPCs) and the formation of new synapses facilitate functional recovery. Extrinsic factors, including neurotrophic factors, cytokines, and extracellular matrix (ECM) molecules, influence the microenvironment at the injury site, modulating inflammation, promoting cell survival, and guiding axonal growth[16]. Moreover, emerging therapeutic approaches such as stem cell transplantation, gene therapy, and pharmacological interventions target specific pathways to enhance neuroprotection, promote axonal regeneration, and mitigate secondary injury mechanisms[15,16]. Harnessing the intricate interplay of intrinsic and extrinsic factors holds promise for optimizing spinal cord recovery pathways and improving outcomes for individuals with SCI[16].

Pharmacological approaches play a crucial role in modulating the complex pathophysiological processes underlying SCI and promoting neural repair[5]. One of the primary targets for pharmacotherapy in SCI is the attenuation of secondary injury mechanisms, including inflammation, excitotoxicity, oxidative stress, and apoptosis[5]. Anti-inflammatory agents, such as methylprednisolone, minocycline, and interleukin-10, mitigate neuroinflammation by suppressing the release of pro-inflammatory cytokines and reducing immune cell infiltration into the injured spinal cord[17]. Furthermore, pharmacological agents targeting excitotoxicity, such as NMDA receptor antagonists (e.g., MK-801, memantine), inhibit glutamate-mediated neuronal excitotoxicity, thereby preventing calcium influx, mitochondrial dysfunction, and subsequent neuronal death[5]. Oxidative stress, another hallmark of secondary injury in SCI, is mitigated by antioxidants like vitamin E, N-acetylcysteine, and edaravone, which scavenge reactive oxygen species and protect neuronal cells from oxidative damage[17]. Moreover, pharmacological modulation of apoptotic pathways, utilizing agents like caspase inhibitors and anti-apoptotic proteins, holds promise for promoting neuronal survival and enhancing functional recovery following SCI[17]. Harnessing the therapeutic potential of pharmacological agents to target specific pathophysiological processes represents a promising approach for improving outcomes in individuals with SCI[5,17].

In addition to targeting secondary injury mechanisms, pharmacological interventions also aim to promote neural repair and regeneration following SCI[14]. Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF), promote neuronal survival, axonal growth, and synaptic plasticity, thus facilitating functional recovery[14].

Administration of exogenous neurotrophic factors or gene therapy to enhance endogenous neurotrophin expression has shown promising results in preclinical models of SCI[19]. Furthermore, agents that modulate the extracellular matrix (ECM), such as chondroitinase ABC (ChABC), disrupt inhibitory scar formation and enhance axonal regeneration by degrading chondroitin sulfate proteoglycans (CSPGs) in the glial scar[20]. Additionally, cell-based therapies utilizing stem cells or progenitor cells offer potential for replacing damaged neural cells, providing trophic support, and promoting tissue repair[18]. While pharmacological approaches hold great promise for enhancing spinal cord repair and functional recovery, further research is needed to optimize treatment strategies, minimize off-target effects, and facilitate translation to clinical practice for the benefit of individuals with SCI[14,18,20].

Furthermore, anti-oxidative therapies may exert neuroprotective effects by modulating signaling pathways involved in cell survival and apoptosis[21]. Nuclear factor erythroid 2-related factor 2 (Nrf2), a key transcription factor regulating the expression of antioxidant and cytoprotective genes, plays a central role in cellular defense against oxidative stress[22]. Activation of the Nrf2 pathway by pharmacological agents such as sulforaphane and dimethyl fumarate enhances antioxidant enzyme activity and promotes neuronal survival following SCI[22]. Additionally, targeting the mitochondria, a major source of ROS production, holds promise for mitigating oxidative damage and preserving cellular function[21]. Mitochondrial-targeted antioxidants, such as MitoQ and SS-31, accumulate within mitochondria and scavenge ROS, thereby preserving mitochondrial integrity and reducing oxidative stress-induced cell death. By modulating antioxidant defense mechanisms and preserving cellular homeostasis, anti-oxidative therapies offer a potential avenue for neuroprotection and neural repair in the context of SCI[21, 22].

Corticosteroids have been a subject of considerable interest in the treatment of SCI due to their potent anti-inflammatory and immunomodulatory properties[23]. One of the most extensively studied corticosteroids in this context is methylprednisolone, which has been investigated for its potential to reduce secondary injury mechanisms and improve neurological outcomes following SCI[24]. Methylprednisolone is believed to exert its therapeutic effects by attenuating inflammation, inhibiting lipid peroxidation, reducing edema, and stabilizing cellular membranes[23]. However, controversy surrounds the use of methylprednisolone due to concerns regarding its safety profile, including the risk of gastrointestinal bleeding, hyperglycemia, infection, and thromboembolic events[23]. Moreover, the optimal dose, timing, and duration of methylprednisolone administration remain subjects of debate, with conflicting evidence regarding its efficacy in improving functional recovery and long-term outcomes in individuals with SCI[24]. While corticosteroids may offer potential benefits in certain clinical scenarios, their use in SCI treatment requires careful consideration of the risks and benefits, as well as adherence to evidence-based guidelines[23, 24].

Non-pharmacological approaches play a vital role in the comprehensive management of SCI, offering adjunctive strategies to enhance rehabilitation, promote neural plasticity, and improve functional outcomes[25]. Physical therapy, occupational therapy, and rehabilitation programs tailored to individual needs are central components of non-pharmacological interventions for SCI[26]. These therapies aim to optimize physical function, facilitate motor recovery, and

promote independence in activities of daily living[26]. Furthermore, assistive technologies such as wheelchairs, orthoses, and functional electrical stimulation devices help individuals with SCI overcome mobility limitations and enhance participation in social and vocational activities[25]. Additionally, emerging non-pharmacological modalities such as transcranial magnetic stimulation (TMS), repetitive transcranial electrical stimulation (rTMS), and locomotor training harness neuroplasticity mechanisms to restore motor function and improve gait in individuals with SCI[25]. By addressing the multidimensional aspects of SCI rehabilitation, non-pharmacological approaches complement pharmacotherapy and contribute to holistic care, ultimately improving the quality of life for individuals living with SCI[25,26].

Neuro-regenerative pathways represent a promising avenue for promoting repair and recovery following SCI[18]. These pathways encompass a complex interplay of cellular and molecular mechanisms involved in axonal regeneration, remyelination, and synaptic plasticity[27]. Key players in neuro-regeneration include neural stem cells, which have the potential to differentiate into various neural cell types and replace damaged neurons, and oligodendrocyte precursor cells, which contribute to remyelination and functional restoration[27]. Additionally, trophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF) promote neuronal survival, axonal growth, and synaptic remodeling[18]. Furthermore, modulation of the extracellular matrix (ECM) composition and inflammatory response at the injury site can create a permissive environment for axonal regeneration and functional recovery[27]. Understanding and harnessing these neuro-regenerative pathways hold promise for developing novel therapeutic interventions aimed at enhancing neural repair and improving outcomes in individuals with SCI[18, 27].

Otherwise, an important consequence of the SCI is the neurogenic shock, which is a form of distributive shock resulting from the disruption of sympathetic nervous system control over vascular tone and heart rate following SCI or severe brain injury[28]. This condition typically arises due to spinal cord trauma at or above the level of the sixth thoracic vertebra, leading to impaired sympathetic outflow and unopposed parasympathetic activity. Consequently, there is widespread vasodilation and bradycardia, resulting in hypotension and decreased tissue perfusion[28]. Neurogenic shock is characterized by a triad of hypotension, bradycardia, and hypothermia, although the latter may not always be present[29]. Prompt recognition and management of neurogenic shock are crucial to prevent complications such as organ hypoperfusion, multiorgan dysfunction, and death. Treatment strategies focus on restoring adequate tissue perfusion through volume resuscitation, vasopressor therapy, and optimizing spinal cord perfusion pressure while addressing associated injuries and maintaining spinal immobilization to prevent further neurological damage[28, 29].

The treatment of neurogenic shock involves a multifaceted approach aimed at restoring adequate tissue perfusion and stabilizing hemodynamics in individuals with SCI induced autonomic dysfunction[30]. Initial management focuses on securing the airway, breathing, and circulation, followed by addressing the specific characteristics of neurogenic shock. In the acute phase, prompt recognition and stabilization of hemodynamic parameters are paramount[31]. Volume resuscitation with intravenous fluids, preferably isotonic crystalloids, is initiated to expand intravascular volume

and improve cardiac preload[30]. However, caution must be exercised to avoid excessive fluid administration, which may exacerbate spinal cord edema and increase the risk of respiratory compromise[31]. Additionally, vasopressor therapy, such as norepinephrine or phenylephrine, is often required to counteract vasodilation and maintain adequate systemic vascular resistance[30]. The use of vasopressors should be titrated carefully to achieve the target mean arterial pressure while minimizing the risk of adverse effects. Close monitoring of hemodynamic parameters, including blood pressure, heart rate, and urine output, is essential for guiding therapeutic interventions and optimizing patient outcomes[31]. In conjunction with hemodynamic support, appropriate spinal immobilization and neuroprotective measures are implemented to prevent further neurological injury and facilitate recovery in individuals with neurogenic shock[30, 31].

Preventing SCI is paramount given its profound impact on individuals, families, and society[9]. Strategies for prevention encompass a multifaceted approach targeting various risk factors and etiologies associated with SCI[9]. Public health initiatives aimed at promoting safety awareness, educating individuals about the risks of high-impact activities, and advocating for the use of protective gear, such as helmets and seat belts, are essential components of SCI prevention[32]. Moreover, implementing engineering solutions to enhance vehicle safety, improving workplace ergonomics, and enforcing regulations to reduce the incidence of falls and violence contribute to preventing SCI[32]. Additionally, advancements in sports medicine, rehabilitation, and assistive technologies play a vital role in minimizing the consequences of SCI and promoting functional independence in individuals at risk[9]. By addressing the modifiable risk factors and adopting proactive measures across multiple domains, concerted efforts toward the prevention of SCI have the potential to mitigate the burden of this devastating condition[9, 32].

CONCLUSION

In conclusion, SCI represents a complex interplay of primary and secondary injury mechanisms, leading to profound sensory, motor, and autonomic dysfunction. Understanding these mechanisms is crucial for the development of targeted therapeutic interventions aimed at mitigating tissue damage and promoting neural repair. Strategies such as soft packing interventions hold promise for modulating scar formation, enhancing axonal regeneration, and promoting functional recovery. Additionally, pharmacological approaches targeting secondary injury mechanisms and promoting neuroregeneration offer potential avenues for improving outcomes in individuals with SCI. Non-pharmacological interventions, including rehabilitation and assistive technologies, complement pharmacotherapy and contribute to holistic care. Furthermore, preventive strategies focusing on safety awareness, engineering solutions, and regulatory measures are essential for reducing the incidence of SCI and minimizing its impact on individuals and society. Overall, a multidisciplinary approach integrating basic science research, clinical trials, and public health initiatives is essential for advancing the field and improving outcomes for individuals living with SCI.

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