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# Completed Clinical Trials Concerning Stem Cell Therapy for Acute Traumatic Spinal Cord Injury

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**ABSTRACT**

Acute spinal cord injury (SCI) is a severe neurological condition limited in treatment options with high morbidity and mortality. This review analyzes the advent of stem cell therapy in the treatment of acute SCI, with a focus on the safety and efficacy of the treatment. Ten clinical trials involving 155 patients were included in this review, encompassing the usage of a multitude of stem cell subtypes with varying doses and a wide range of treatment timelines. Of the 155 patients across the included clinical trials, 70 (45%) of the patients exhibited an improvement of one or more American Spinal Injury Association impairment scale grade (AIS) and no patients exhibiting worsening of grades. Adverse events (AEs) documented in the trials were mild and unrelated to treatments, and two of the ten trials reporting occurrences of serious adverse events (SAEs) that were possibly related to the stem cell intervention. Improvement in sensory, motor, and neurological function were prevalent across the studies, with certain studies highlighting improvements in patient quality of life (QOL). Although the study's results were promising, significant conclusions are unable to be made due to the nature of the limitations in many of the studies. Limitations included small sample sizes; non-randomized, non-controlled studies; high heterogeneity within the trials; lack of randomization; limited standardization within the trials; and incomplete reporting on both safety and efficacy outcomes in certain cases. Future research and development in the field should focus on large-scale, multicenter, randomized and controlled trials with standardized protocols to ensure significant analysis of results and outcomes. Stem cell therapy in the treatment of acute SCI represents a newly forged and promising avenue in regenerative medicine that has the potential to improve an array of patient outcomes and the field of SCI treatment.

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## Introduction

Spinal cord injury (SCI) is a detrimental traumatic neurological issue that carries tremendous morbidity and mortality. SCI is characterized by partial or complete damage to the spinal cord resulting in transient or permanent alterations of neurological and/or motor function [1]. The prevalence of SCI in the United States has been estimated to be approximately 305,000 persons and 15.4 million worldwide, with vehicular crashes being a lead cause of the issue [2,3]. SCI carries immense disability burden with an average of 18% of people with SCI being employed 1-year post-injury and an average lifetime cost of two million dollars and above [2].

The high morbidity and mortality associated with SCI is due to the vital functions served by the spinal cord as a conduit for communication between the central nervous system and the rest of the body. Disruption to the spinal cord results in loss of both sensory and motor function below the site of injury depending on its severity. Acute SCI is characterized by a sudden insult to the spinal cord resulting in loss of motor and neurological function with no prior injury or degeneration of the spinal cord [4]. An SCI is typically defined as acute if the timeframe of injury and resultant damage falls in 2 hours to 2 weeks. This primary injury is marked by hemorrhage, ischemia and inflammation of the damaged area [4]. Chronic SCI is caused by an initial acute insult to the spine and long-lasting effects (greater than 6 months) or long-standing degeneration of the spinal cord, the latter being non-traumatic in etiology and the former being traumatic. The usage of the term "chronic" in SCI implies the stabilization of the primary injury as it is undergoing little change [5]. This phase is marked by maturation and stabilization of glial scars at the lesion site [6].

Imaging of the patient in the hyperacute phase is vital to determine the diagnosis and facilitates management of the injury. It is generally accepted that life-threatening injuries that affect the patient's airways, breathing, and circulation should be managed first before SCI. Goals of surgical management of SCI are to stabilize the spine, decompress the spinal canal, and prevent further injury to the nervous system [7]. The improvement and outcomes to a patient's motor and neurological systems following emergent decompressive surgery is still up for debate, however, the practice is widely utilized [7]. Current findings show no pharmacological interventions are successful at stabilizing and preventing further neurological damage following SCI [7]. The amount of motor, sensory, and neurological disability is dependent on the severity and level of SCI. The American Spinal Injury Association (ASIA) impairment scale is typically employed to classify severity of the SCI. The ASIA scale is a standardized examination ranking the severity of SCI from levels A-E, with A characterized by complete impairment and loss of motor or sensory function while E is characterized by normal motor and sensory function [8].

The lifelong morbidity of SCI is primarily due to the nearly negligible amount of spinal cord regeneration post-SCI. The adult central nervous system (CNS) is a relatively stable feature of the

body, with limited regenerative mechanisms at its disposal. It has been proposed that the spinal cord has evolved regenerative mechanisms that are suppressed by both intrinsic and extrinsic factors but can be activated by injury [9]. Spontaneous motor and neurological recovery via intrinsic pathways following SCI is variable and transient, and external interventions are needed to improve outcomes [10]. Leading interventions with the goal of maximizing spinal cord regenerative capabilities include lithium treatment, cell therapy, biomaterial transplantation, bioactive substance regulation, and physical controlling [10]. In this paper we will be discussing the advent of stem cell therapy in SCI patients, specifically the safety and efficacy of stem cell interventions in clinical trials for SCI treatment.

Stem cells are a subset of undifferentiated somatic or embryonic cells with the unique capability for self-renewal, sustained proliferation, and multi-directional specialization [11]. The primary types of stem cells utilized in SCI regeneration include mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), bone marrow stem cells (BMSCs), and neural stem cells (NSCs). MSCs are stromal cells derived from a variety of tissue types with the ability to self-renew and exhibit multi-directional differentiation [12]. iPSCs are derived from the patient's own somatic cells, incubated with a unique set of transcription factors, inducing the cells to de-differentiate into pluripotent progenitor cells [13]. The bone marrow is the only reservoir of stem cells in the human body, holding a variety of stem cell subtypes, including hematopoietic stem cells and MSCs among others [14]. NSCs are especially important in the lesion microenvironment following SCI, preserving tissue integrity and supplying neurotrophic support to neurons at the site of injury [15].

The microenvironment of the spine following traumatic SCI is hostile as multicellular interactions and disruption of CNS mechanisms leads to the formation of a dense and fluid-filled glial scars [16,17]. Glial secretory factors pose a risk to initially undamaged structural and neuronal cells near the site of injury, leading to inhibition of myelination and axonal generation and promotion of immune cell infiltration leading to sustained inflammation [16]. However, glial scars have recently been found to be beneficial in the chronic rehabilitation of the spine as inhibition of scar formation was found to greatly reduce regeneration of ascending sensory tract axons [18]. There lies a delicate balance between the positive and negative outcomes of glial scar formation following SCI that must be deciphered to improve the regenerative potential of the spine following injury. Stem cells have been proposed as an intervention due to their ability to modulate neuronal and structural apoptosis and glial scar formation as well as reconstituting the lesion microenvironment. For example, MSC intervention in animal models following SCI have exhibited potential to strengthen the blood brain barrier (BBB) and reprogram inflammatory macrophages toward an anti-inflammatory lineage [19]. Stem cells also can stimulate plasticity in the CNS and enhance the expression of genes in the spinal cord to prevent further secondary injury following SCI. In a rodent model of SCI, stimulation of transplanted iPSCs enhanced the expression of synapse-related genes and proteins surrounding the host tissue lesions site, improving locomotor function [20]. Several stem cell subtypes, especially MSCs, have a unique secretome that aid in both immunomodulation as well as regenerative processes. Their immunomodulation effects stem from their ability to secrete a wide spectrum of soluble factors such as cytokines, enzymes, and nitric oxide [21]. The interactions between the stem cells and regulatory T-cells and monocytes play a key role in immunomodulation, suppressing inflammation and sustaining a more stable microenvironment for repair and regeneration.

Human clinical trials concerning the intervention of stem cells in the treatment of SCI are relatively sparse. This brings about issues about validity of results as well as questions that remain to be unanswered due to the lack of data and knowledge on the subject. One of the primary knowledge gaps present in stem cell interventions for SCI is if the efficacy of infusion decreases over time. In addition to the optimal timing of therapeutic intervention is whether improved outcomes are more likely in patients with higher AIS (ASIA Impairment Scale) grades. Other mechanistic and physiological factors are still yet to be answered, such as ensuring survival in the harsh microenvironment of the lesion and which subtype of stem cells present the best overall outcomes. The primary outcomes of this review on human clinical trials in stem cell intervention for acute SCI are the safety and efficacy of the procedures and providing insight on some of these knowledge gaps.

The primary outcome of this review is assessing the safety of stem cell intervention in the treatment of acute SCI. This outcome was measured through collection and analysis of adverse events (AEs) and serious adverse events (SAEs) related to the intervention's procedure. These AEs and SAEs are any unfavorable medical occurrence in a patient throughout the course of the trial, whether it be related to treatment or stemming from an unrelated issue.

The secondary outcome of this review is assessing the efficacy of stem cell intervention in the treatment of acute SCI. This outcome was measured through extraction and analysis of the American Spinal Association Injury (ASIA) impairment scores at the beginning and at the conclusion of the clinical trials. The purpose of the ASIA scale is to standardize documentation of SCI, guide further imaging and treatment, and determine the complete or incomplete nature of the injury [21]. The scale ranges from A-E. Grade A denotes a complete SCI with no motor or sensory function in the sacral segments (S4-S5) of the spinal cord. Grade B denotes an incomplete SCI with sensory function preserved but motor function is absent below the neurological level in the sacral segments. Grade C denotes an incomplete SCI with motor function preserved below the neurological level and more than half of key muscles below the neurological level having a muscle grade less than 3. Grade D denotes an incomplete SCI with preserved motor function below the neurological level and at least half of key muscles below the neurological level having a muscle grade of 3 or more. Grade E denotes normal motor and sensory function.

**Methodology**

Candidate clinical trials were identified through searches of the PubMed, Cochrane, Embase, ClinicalTrials.gov, and WHO databases. The following terms were combined to generate search keywords: (Spinal cord injury OR acute spinal cord injury OR spinal cord contusion OR spinal cord compression OR SCI) AND (stem cell OR stem cells OR stem cell therapy OR stem cell transplantation OR cell therapy).

Inclusion criteria for the clinical trials include patients with acute SCI, stem cell interventions regardless of subtype, AIS grades measured for outcomes, adverse events recorded as primary/secondary outcome. Exclusion criteria for clinical trials are as follows: no AIS grades collected at study inception or conclusion.

## Results and Discussion

Table 1 and 2 exhibit the characteristics and results of the 10 studies included in this study, of which 7 were clinical trials, 2 were case series, and 1 being a pilot study. Participant ages ranged from 18 to 75 years, with large variability between the studies. these data are an estimate due to one study, Chhabra S. et. al., not providing age of the participants [22-24].

**Table 1: Characteristics of Clinical Trials included in the Current Study**

| Article | Country of Origin | Mean Age | Sample Size | Injury Level | Time Between Injury and Injection | Stem Cell Subtype | Route of Administration | Mean Dosage |
|---|---|---|---|---|---|---|---|---|
| Attar A et. al., [22] (2011) | Turkey | 22 | 4 | Thoracic | ≥14 Days | Autologous Bone Marrow Mononuclear Cells | Intralesionally | $245.9 \times 10^6 \pm 272.8 \times 10^6$ |
| Bydon M et. al., [23] (2024) | United States | 34.6 | 10 | Cervical, Thoracic | 7-22 Months | Adipose Derived-Mesenchymal Stem Cells | Intrathecal | $100 \times 10^6$ |
| Chhabra S et. al., [24] (2016) | India | NA | 21 | Thoracic | 10-14 Days | Bone Marrow Cells | Intravenous, Intrathecal, Intralesionally | $200 \times 10^6$ |
| Fessler G et. al., [25] (2022) | United States | 31.8 | 25 | Cervical | 14-30 Days | Oligodendrocyte Progenitor Cells (LCTOPC1) | Intraparenchymal | $1.24 \times 10^6 \pm 7.67 \times 10^6$ |
| Honmou O et. al., [26] (2021) | Japan | 46.9 | 13 | Cervical | 43-54 Days | Mesenchymal Stem Cells | Intravenous | $1.25 \times 10^8 \pm 0.24 \times 10^8$ |
| Jiang C et. al., [27] (2013) | China | 41.1 | 20 | Cervical, Thoracic, Lumbar, Sacral | 3 months to 10 years | Bone Marrow-derived Mesenchymal Stem Cells | Intralesionally | $1 \times 10^8$ |
| McKenna L et. al., [28] (2022) | United States | 26.5 | 5 | Thoracic | 7-14 Days | Oligodendrocyte Progenitor Cells (LCTOPC1) | Intraparenchymal | $2 \times 10^6$ |
| Saini R et. al., [29] (2022) | India | 28.1 in Experimental, 32.6 in control | 13 | NA | 7-17 Days | Bone Marrow-derived Stem Cells | Intramedullary | $2 \times 10^8$ |
| Shin C et. al., [30] (2015) | Republic of Korea | 37.2 | 34 | Cervical | 16-213 Days | Fetal Brain-Derived Neural Stem Cells | Intramedullary | $1 \times 10^8$ |
| Smirnov A et. al., [31] (2022) | Russia | 41.9 | 10 | Cervical, Thoracic, Lumbar | 2-3 Days | Human Umbilical Cord Blood Cells | Intravenous | $1.13 \times 10^9 \pm 0.21 \times 10^9$ |

**Table 2: Preoperative and Postoperative Patient Outcomes and Adverse Events**

| Article | Preoperative AIS Grade | | | | AIS Grade Improvement | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | Yes | No | Follow Up Time | Adverse Events | Serious Adverse Events |
| Attar A et. al., [22] (2011) | 4 | 0 | 0 | 0 | 3 | 1 | 1 year | 0 | 0 |
| Bydon M et. al., [23] (2024) | 8 | 2 | 0 | 0 | 8 | 2 | 96 Weeks | 44 | 0 |
| Chhabra S et. al., [24] (2016) | 21 | 0 | 0 | 0 | 0 | 21 | 1 year | 1 | 0 |
| Fessler G et. al., [25] (2022) | 15 | 10 | 0 | 0 | 8 | 17 | 1 year | 534 | 29 |
| Honmou O et. al., [26] (2021) | 6 | 2 | 5 | 0 | 12 | 1 | 6 months | 0 | 0 |
| Jiang C et. al., [27] (2013) | 8 | 4 | 8 | 0 | 15 | 5 | 30 Days | NA | NA |
| McKenna L et. al., [28] (2022) | 5 | 0 | 0 | 0 | 0 | 5 | 5 years | 174 | 4 |
| Saini R et. al., [29] (2022) | 13 | 0 | 0 | 0 | 9 | 4 | 6 months | NA | NA |
| Shin C et. al., [30] (2015) | 30 | 4 | 0 | 0 | 6 | 28 | 1 year | 0 | 0 |
| Smirnov A et. al., [31] (2022) | 6 | 4 | 0 | 0 | 9 | 1 | 1 year | 419 | NA |
| TOTAL | 116 | 26 | 13 | 0 | 70 | 85 | | 1172 | 33 |

*The American Spinal Injury Association Impairment Scale is used by first-responders and physicians to gauge the severity of an SCI. The scale ranges from A-E, with A denoting a complete SCI with no motor or sensory function below the site of injury and E denoting normal motor, sensory, and neurological function.

All studies included patients with acute traumatic spinal cord injuries. Six patients from Jiang C et. al., experienced spinal cord injuries of non-traumatic etiology [27]. The most affected spinal cord level was thoracic, followed by cervical, lumbar, and sacral.

Of the 10 studies reviewed, 3 studies utilized bone marrow derived stem cells, 3 utilized mesenchymal stem cells, 2 utilized oligodendrocyte progenitor cells, 1 used umbilical cord blood cells, and 1 used neural stem cells. Most studies used a route of administration of stem cells directly into the CNS either through intrathecal, intramedullary, intraparenchymal, or intralesional injection. The remaining studies used an intravenous route of administration. One study, Chhabra S. et. al., used a mix of the routes in the administration [24]. Dosages across all 10 studies were highly variable, with some studies utilizing a standardized dose amongst all subjects, others featuring a dose-escalation strategy, and others having no standardized dosing regimen.

The most common AIS grade in these acute traumatic SCI cases was A (74.84%), followed by B (16.77%), and C (8.39%). The higher frequencies of AIS grade A and B in most of these studies could be due to the higher incidence of traumatic SCI in these grades. Additionally, many of the included studies excluded patients with AIS grades of C and below. This is most likely due to the extent of the neurological damage and potential to acquire significant results due to the intervention of stem cells rather than spontaneous neurological recovery.

The primary efficacy parameter measured in this review of studies was improvement in AIS grade from the start of the study to the end. Of the 155 patients across the 10 studies included, 70 patients improved by one grade or more (45.16%), 85 showed no improvement (54.84%), and 0 patients worsened. Improvement within studies ranged from 0% out of 21 subjects in Chhabra S. et. al., to 90% out of 10 subjects in Smirnov A. et. al., 2 of the 10 studies, Shin J. et. al., and Saini R. et. al., were controlled trials [24, 29-31]. 5 patients out of 19 (26.3%) in the transplantation group in Shin J. et. al., exhibited improvement in AIS grades compared to 1 in 15 (6.67%) in the control group. 7 out of 7 (100%) patients in the transplantation group in Saini R. et. al., exhibited improvement in AIS grades compared to 3 out of 6 (50%) in the control group [29,30].

Adverse events (AEs) and serious adverse events (SAEs) were primary safety parameters when conducting the review of these studies. The only studies reporting SAEs were reported in Fessler R. et. al., and Mckenna L. et. al., 29 SAEs were reported in Fessler R. et. al., with 2 of the 29 reported as having a possible link to the intervention [25,28]. One SAE was possibly linked to the administration of tacrolimus, a potent immunosuppressive, following implantation as the patient experienced a bacterial infection. The other SAE was possibly linked to the injection procedure as the patient experienced cerebrospinal fluid (CSF) leakage. Of the 4 SAEs recorded in Mckenna L. et. al., 0 were related to the procedure [28]. Five studies contained patients who reported AEs throughout the duration of the trial. Bydon M. et. al., reported 44 AEs in the 96-week trial duration, 17 of which (37%) were considered possibly related to the intervention [23]. Chhabra H. et. al., reported one AE; a liver abscess not related to the stem cell procedure [24]. Fessler et. al., reported 534 AEs, of which 1 (0.19%) possibly related to the intervention [25]. McKenna et. al., recorded 174 total AEs, of which 25 (14.4%) were possibly related to the intervention [28]. Smirnov et. al., reported a total of 419 AEs throughout the trial, of which 2 AEs (0.5%) were possibly related to the intervention [31]. Of the 10 studies included in this review, 2 studies did not report on patient AEs or SAEs.

There were several limitations in the process of conducting this review. The primary limitation in the field of stem cell therapy for traumatic spinal cord injury is the novelty of the intervention. Most of the clinical trials concerning this field of stem cell therapy are in progress or are currently recruiting patients. This limits the availability of data on the subject and prevents statistically supported conclusions to be drawn. In addition to this limitation, many of the clinical trials that have been published lack control groups. This prevents the direct comparison of the stem cell intervention to a placebo treatment, making it impossible to determine if results are due to the intervention or other factors. Many of the studies lack randomization, feature variability in dosages, high heterogeneity in the cohorts, and fail to report on AEs or patient outcomes. These shortcomings are likely due to the small sample sizes present in the studies and novelty of the intervention, but they do not allow for conclusions regarding stem cell therapy in SCI treatment to be drawn.

As the field of regenerative medicine in the treatment of acute spinal cord injury grows and the quality of clinical trials regarding this topic improves, multiple factors and outcomes should be put at the forefront. There was an overall improvement of one or more AIS grades in 45% of the 155 patients included across the 10 clinical trials. Although there is a wide degree of heterogeneity among the clinical trials; including the preoperative AIS grades, follow-up times, cell dosage, and others, this is a significant statistic. Efficacy is one of the primary outcomes measured in clinical trials surrounding stem cell therapy for SCI. This statistic provides future researchers with the knowledge that the intervention shows efficacy and the trials on the subject should be expanded. What many of the studies have in common are their conclusions; with future clinical trials urged to expand the number of participants, randomize and control the trials to improve the analysis of the data, and focus on homogeneity in the selection process of future clinical trials. These conclusions aim to improve statistical analysis of the acquired data in the trials and provide definitive conclusions on the efficacy of the treatment.

One of the primary morbidities in SCI is quality of life (QOL) impairment. Patients suffer from loss of mobility, urinary and bowel dysfunction, and in severe cases, the inability to accomplish daily tasks on their own. Only 2 of the 10 clinical trials reviewed explicitly discussed QOL outcomes in the patients. In the 2022 study conducted by Saini et. al., patients experienced marked improvements in bladder sensation, posture control, and decreased spasticity [29]. In the 2013 study conducted by Jiang et. al., 8 out of the 10 patients experienced improved micturition function and 6 out of 10 patients experienced improved bowel function [27]. These are very important outcomes to focus on as the ability to execute these functions and live independently diminishes future sequelae and the financial burden of the injury. This introduces the price of the stem cell treatment and its associated costs.

Cost of care for SCI varies widely and is dependent on several factors including AIS grade, concomitant injuries, and in-hospital complications. In a review studying cost analysis of SCI treatment, acute care of SCI ranges from $290 to $612,590; the first year following the injury ranges from $32,240 to $1,156,400; and the following years ranging from $4,490 to $251,450 [32]. Explicit monetary values for the intervention of stem cell therapy for SCI are difficult to find due to the novelty of the treatment and the fact that the treatment is still under trial. Individual studies focusing on the treatment of neurological issues with stem cell

therapy have concluded that differences in cell type do not have a significant impact on clinical outcomes [33]. A study published in 2018 found that large-scale manual manufacturing of MSCs had a production cost of $2,056.85 per dose of 100 x $10^6$ cells and $205,684.85 to manufacture 100 doses [34]. Another study analyzing the cost-effectiveness of MSC therapy found that one administration of allogeneic MSCs had an expected total cost of $13,536 [35]. Various factors may increase or decrease the cost of the intervention, including the number of doses, route of administration, and the autologous or allogeneic source of the cells. Although the intervention may be costly, the potential for regeneration and recovery of motor and sensory functions diminishes DALYs (disability-adjusted life year) and improves functional independence. This improvement in functional independence allows patients to return to work and prevent further incurrence of direct treatment costs related to SCI.

The discussion of the cost of stem cell therapy in SCI requires the topic of equity in the field of regenerative medicine to be touched on. Two out of the ten clinical trials included within this review were conducted in India, which is classified as a low- and middle-income country (LMIC). Due to the high cost of procurement, storage, and modification of stem cells, LMICs have been slow to adopt the advent of stem cell therapy. A benefit of stem cell therapy compared to traditional treatment to SCI is its reduction of financial burden to the patient, either through reduced indirect operative costs to the patient or reduced time out of the labor force [36]. These outcomes are especially important in LMIC due to the immense financial burden of SCI, both in the direct treatment of the injury and indirect cost of loss of productivity. The advent of stem cell therapy for SCI, an already expensive illness to treat, may intensify the current disparities of healthcare in underserved populations [37,38]. Future clinical trials and research should focus on the cost-effectiveness of stem cell therapy in SCI in addition to the safety and efficacy of the treatment. Ensuring equitable access for the utilization of stem cell treatment in SCI in diverse healthcare settings requires reductions in procurement of stem cells and generalizability of the treatment.

## Conclusion

The implementation of stem cell therapy in acute spinal cord injury holds much promise in the developing field of regenerative medicine. Positive results outlined both the safety and efficacy of this novel intervention. Eight of the ten clinical trials included in this review of stem cell therapy in the treatment of acute spinal cord injury exhibited patient improvement of AIS grades. Few adverse and serious adverse events reported across the studies included were possibly related to the stem cell treatment. Many of the patients included in the study experienced improvements in sensory, motor, and neurological function following stem cell treatment. These factors contribute to the improved quality of life that is often absent in traditional therapies for acute spinal cord injury. Through conducting this review, it can be concluded that stem cell therapy is considered promising in the treatment of spinal cord injury based on patient outcomes derived from the clinical trials included in this study. Although this conclusion is based on favorable results from these studies, the studies experienced multiple limitations that must be addressed to ensure statistically significant results in the future and the transition of the treatment from research to clinical practice. These improvements include larger patient cohorts; randomized, multicenter, controlled trials with standardized procedures and dosages across all subjects; and improved outcome measures that focus primarily on patient outcomes as the safety and efficacy of the intervention have been promising.

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