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Current status and future perspectives on stem cell transplantation for spinal cord injury

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Abstract

BACKGROUND

Previous assessments of stem cell therapy for spinal cord injuries (SCI) have encountered challenges and constraints. Current research primarily emphasizes safety in early-phase clinical trials, while systematic reviews prioritize effectiveness, often overlooking safety and translational feasibility. This situation prompts inquiries regarding the readiness for clinical adoption.

AIM

This study seeks to offer an up-to-date systematic literature review of clinical trial results concerning stem cell therapy for SCI.

METHODS

A systematic search was conducted across major medical databases [PubMed, Embase, Reference Citation Analysis (RCA), and Cochrane Library] up to October 14, 2023. The search strategy utilized relevant Medical Subject Heading (MeSH) terms and keywords related to "spinal cord", "injury", "clinical trials", "stem cells", "functional outcomes", and "adverse events". Studies included in this review consisted of randomized controlled

trials and non-randomized controlled trials reporting on the use of stem cell therapies for the treatment of SCI.

RESULTS

In a comprehensive review of 66 studies on stem cell therapies for SCI, 496 papers were initially identified, with 237 chosen for full-text analysis. Among them, 236 were deemed eligible after excluding 170 for various reasons. These studies encompassed 1086 patients with varying SCI levels, with cervical injuries being the most common (42.2%). Bone marrow stem cells were the predominant stem cell type used (71.1%), with various administration methods. Follow-up durations averaged around 84.4 months. The 32.7% of patients showed functional improvement from AIS A to B, 40.8% from AIS A to C, 5.3% from AIS A to D, and 2.1% from AIS B to C. Sensory improvements were observed in 30.9% of patients. A relatively small number of adverse events were recorded, including fever (15.1%), headaches (4.3%), muscle tension (3.1%), and dizziness (2.6%), highlighting the potential for SCI recovery with stem cell therapy.

CONCLUSION

In the realm of SCI treatment, stem cell-based therapies show promise, but clinical trials reveal potential adverse events and limitations, underscoring the need for meticulous optimization of transplantation conditions and parameters, caution against swift clinical implementation, a deeper understanding of SCI pathophysiology, and addressing ethical, tumorigenicity, immunogenicity, and immunotoxicity concerns before gradual and careful adoption in clinical practice.

INTRODUCTION

Each year, approximately half a million fresh cases of spinal cord injury (SCI) emerge on a global scale. These instances are predominantly triggered by trauma stemming

from car accidents, slips, firearm incidents, or medical/surgical complications. Given the nature of these causative factors, SCI primarily affects younger individuals.[1]

The intricate and time-sensitive pathophysiology of SCI renders the exploration of therapeutic targets exceedingly challenging. Following the initial mechanical injury, a cascade of secondary events exacerbates patients' conditions. These events include the inflammatory response, gliosis hyperplasia, the creation of inhibitory environments, and the formation of scars, all of which hinder axonal regeneration and limit the effectiveness of various treatment approaches.[2] These pathophysiological consequences often lead to enduring neurological impairments, including the loss of motor and sensory functions below the injury level, as well as autonomic dysfunction.[3]

Present-day clinical approaches prioritize prompt surgical decompression and mechanical stabilization at the location of SCI, bolstered by pharmaceutical measures encompassing methylprednisolone, nimodipine, naloxone, and various others. Subsequent to this crucial stage, patients engage in rehabilitative initiatives geared towards reinstating functionality and self-sufficiency. Regrettably, these endeavors yield unsatisfactory results concerning the safeguarding of neural structures, the rejuvenation of nervous tissue, and the recuperation of bodily functions. The primary cause of this dearth of achievement can be attributed to the intricate pathophysiological processes inherent to SCI, culminating in irreversible harm within the neural microenvironment at the site of injury.[4,5]

In recent decades, stem cell therapy has emerged as a highly promising avenue within the realm of SCI. After a series of encouraging experimental treatments using diverse stem cell types in animals of various species, clinical trials involving human SCI patients became a reality in the early 2000s.[3,5]

While prior evaluations of stem cell therapy for SCI have occurred, they have encountered specific challenges and restrictions. Most current investigations consist of single-arm, early-phase clinical trials primarily aimed at gauging the safety of stem cell treatments. In contrast, established systematic appraisals have exclusively featured randomized controlled trials, concentrating solely on the effectiveness of stem cells.

Consequently, they have encompassed a limited range of studies and do not provide a comprehensive scrutiny of available data. Furthermore, they overlook critical facets such as the safety and feasibility of translating stem cell therapy from laboratory research to clinical application. Consequently, the question of whether we have amassed enough substantiation to justify an immediate clinical adoption of stem cell therapy remains open.[6,7]

This review, in turn, delves into the pathophysiological intricacies of SCI, exploring the potential mechanisms through which various stem cells contribute to the restoration of the spinal cord, and it presents the fundamental characteristics and results of the pertinent clinical trials published.

MATERIALS AND METHODS

Literature review

The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[8] Two authors (E.A. and A.P.) performed a systematically comprehensive literature search of the databases PubMed, Web of Science, Cochrane, Embase databases, and Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). The first literature search was performed on August 30, 2023, and the search was updated on October 14, 2023. A combination of keyword searches was performed to generate a search strategy. The search keywords, including "spinal cord", "injury", "clinical trials", "stem cells", "functional outcomes", and "adverse events", were used in both AND and OR combinations. Studies were retrieved using the following Medical Subject Heading (MeSH) terms and Boolean operators: ("spinal injury" OR "spinal cord injury") AND ("stem cells" OR "staminal cells") AND ("clinical trials" OR "clinical studies"). Other pertinent articles were identified through reference analysis of selected papers. A search filter was set to show only publications over the designated period, 2010–2023.

Inclusion and exclusion criteria

The studies were chosen according to the below inclusion criteria: 1) The use of English; 2) clinical trials, such as randomized controlled or non-randomized controlled trials, single-arm or double-arm studies; 3) research on the use of stem cells to treat spinal cord injuries; 4) research with adverse occurrences or functional results. The subsequent criteria for exclusion were utilized: 1) publications such as editorials, case reports, case series, cohort studies, literature reviews, and meta-analyses; 2) research with vague methodology and/or findings; 3) research that omits information on adverse occurrences or functional results; 4) study that has been published several times; 5) The complete text is not available; 6) Patients with various significant conditions are included. Duplicates were eliminated from the list of recognized studies before importing it into Endnote X9. E.A. and P.P.P., two independent researchers, examined the data in accordance with the inclusion and exclusion criteria. All differences were settled by M.Z., the third reviewer. After that, full-text screening was applied to the qualifying articles.

Collecting data

We extracted the following data for each study: authors, year, stage of the clinical trial, number of patients, degree of damage, neurological status prior to treatment, type and origin of stem cells, dosage and mode of administration, duration of follow-up, and clinical results.

Outcomes

Our primary outcomes were: 1) clinical improvement, evaluated by the American Spinal Cord Injury Association Impairment Scale (ASIA) improvement scale (AIS) (Table 1), or, if not available, with other spinal cord injury scales or reported descriptive clinical data; 2) Adverse events (AEs) pertaining to many systems such as the cardiovascular, neurological, digestive, and musculoskeletal systems.

Assessment of bias risk

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS).[9] By evaluating the study's comparability, outcome evaluation, and selection criteria, quality assessment was carried out. Nine was the optimal score. Better study quality was reflected by higher ratings. Research that scored seven or above were deemed to be of excellent quality. Independently, E.A. and P.P.P. conducted the quality evaluation. The third author reexamined publications when inconsistencies emerged (Figure 1).

Analytical statistics

Ranges and percentages were included in the descriptive statistics that were provided. The R statistical software, version 3.4.1, was used for all statistical analyses (http://www.r-project.org).

RESULTS

Literature review

After duplicates were eliminated, 496 papers in total were found. 237 articles were found for full-text analysis after title and abstract analysis. It was determined who was eligible for 236 articles. The following criteria led to the exclusion of the remaining 169 articles: (1) unrelated to the study topic (164 articles); (2) lacking methodological and/or outcome information (2 articles); and (3) a systematic review or meta-analysis of the literature (3 articles). For each of the patient groups under consideration, at least one or more outcome measures were available for all of the studies that were part of the analysis. The PRISMA statement's flow chart is depicted in Figure 2.

The PRISMA checklist is offered as additional content.

Data Analysis

This table presents data from a comprehensive collection of 67 studies that explored the use of stem cell therapies for spinal cord injuries. In total, these studies encompassed 1086 patients with varying injury levels. Cervical injuries were the most prevalent (42.2%), followed by thoracic injuries (32.3%), and lumbar injuries (8.6%). The specific stem cell types used varied across the studies, with bone marrow stem cells (BMSC) being the most common (71.1%), followed by umbilical cord tissue stem cells (UCMSC) in 16%, and others. The treatment approaches included intrathecal administration (61.3%), intramedullary (29.3%), and intravenous or intravenous plus intralesional methods (9.7%).

The follow-up periods for these studies ranged from acute to chronic stages, with an average follow-up duration of approximately 84.4 months. The outcomes of these treatments were generally positive, with 32.7% of patients showing functional improvement from AIS A to B, 40.8% from AIS A to C, 5.3% from AIS A to D, and 2.1% from AIS B to C. A small percentage (1.3%) experienced improvement in AIS B to D, and AIS B to E (1.3%). Furthermore, sensory improvements were observed in 30.9% of patients. In terms of AEs, the studies consistently reported a low occurrence, with only mild and transient issues. Fever was experienced by 15.1% of patients, while 4.3% reported headaches, 3.1% experienced a transient increase in muscle tension, and 2.6% had dizziness. These findings collectively highlight the potential for functional recovery in spinal cord injury patients through stem cell therapies while underscoring their relatively safe profile (Tables 2-5).

DISCUSSION

The number of clinical trials involving stem cells has significantly increased in the last few years. Thousands of registered trials claim to use stem cells in their experimental treatments across the globe.[2, 4, 7, 10] This could imply that stem cell therapy has a strong and established track record in clinical practice. But in actuality, even with some noteworthy breakthroughs, the application of stem cells in medicine is still relatively new.12, 15 Phase I clinical trials, case series, and case reports make up the majority of

stem cell clinical research conducted today.[2,4,5] Good randomized controlled trials are hard to come by, and even simple controlled trials are difficult to find. It is therefore difficult to assess the efficacy of stem cells through head-to-head comparisons using meta-analysis. Furthermore, even while differences in patient age, the degree of spinal cord injury, cell kinds, sources, culture conditions, and other variables might make inter-study comparisons more difficult, they are nevertheless essential.[5,8,9,11-15]

Our review reveals a general enhancement in patient functionality, encompassing both motor and sensory perspectives. Notably, 32.7% of patients exhibited functional improvement, transitioning from AIS A to B, and 40.8% from AIS A to C. Sensory improvements were observed in 30.9% of patients. However, these improvements represent only modest progress in sensory and motor function, falling short of the anticipated levels required for walking and daily activities. It's important to highlight that the assessment of sensory and motor function, based on the ASIA score, depends on subjective evaluations by both the assessor and the patient, which introduces a degree of result variability.[16,17] Although the high effectiveness rates seem encouraging, the lack of control groups in the majority of trials allows for the possibility that the therapeutic improvements after stem cell transplantation might be influenced by spinal cord decompression or spontaneous healing. Consequently, stem cells cannot be fully blamed for the therapeutic benefits. Therefore, thorough investigation into the true therapeutic effects of stem cells is necessary using standardized controlled trials that follow pertinent regulations.[17-21]

The potential benefits of stem cell therapy for patients remain uncertain, compounded by suboptimal design and execution of clinical trials.[12,22] Rigorously conducted randomized controlled trials, featuring double-blind methodologies and placebo groups, offer the most precise and dependable data, surpassing observational studies or case reports in reliability. Nonetheless, the majority of ongoing investigations consist of observational studies, case series, and similar approaches.[15,21] Clinical trials often suffer from issues such as limited sample sizes and subpar quality.[22,23] Furthermore, a considerable portion of the studies reviewed were phase I clinical trials, typically

focused on evaluating stem cell safety. Intriguingly, all of these studies primarily explored and reported on the effectiveness of stem cells while neglecting to document AEs. Consequently, the safety profile of stem cells could potentially be inaccurately elevated.[17]

The utmost priority should always be the safety of patients. The safety of stem cell therapy and the occurrence of AEs primarily hinge on the inherent traits of the transplanted stem cells and the transplantation procedure.[16,17] Our review of the studies did not reveal any severe AEs, such as the formation of tumors, further reinforcing the claims of these studies regarding the safety of stem cell therapy. Nevertheless, it's crucial to recognize that the absence of serious AEs doesn't definitively establish the therapy's safety. Many AEs were documented in the 66 research that we looked at. These included effects on the neurological, musculoskeletal, digestive, and cardiovascular systems. Following the proper medical measures, the majority of these AEs were moderate, and the patients recovered well. It would be premature, nevertheless, to declare stem cell treatment safe in all cases. By doing thus, it might unintentionally encourage unjustified trust in the therapy and jeopardize the scientific assessment of its safety and efficacy. Furthermore, Aspinall et al.'s analysis revealed that only thirty percent of clinical trials sufficiently recorded different adverse events (AEs) during the clinical trial.[24] Consequently, it's plausible that a sizable percentage of studies may have failed to disclose or ignored AEs in an effort to make stem cell treatment appear safer than it actually is.

Among the myriad safety concerns associated with stem cell transplantation, the specter of tumorigenesis looms larger and more ominous than the comparatively milder fever and neuropathic pain stemming from immune or allergic reactions.[17,22,23,25] Stem cell products bear the highest potential for tumorigenesis due to the presence of lingering undifferentiated stem cells, cells carrying malignant transformations or mutations, and genetic instability.[26] Moreover, the expression of foreign genes, such as different growth factors, might result in oncogenic activation, and the danger of insertional mutagenesis in stem cells is introduced by genetically modified viral vectors, such as lentiviruses

and retroviruses. It's worth noting that there exists no consensus on a global scale regarding risk assessment strategies for evaluating the tumorigenicity and oncogenicity of stem cells. Curiously, there have been no reports of severe adverse events, including tumorigenesis, in clinical trials thus far. However, this absence of reports might be attributed to the relatively brief follow-up period.[16,17,24]

While preclinical studies have indeed established a solid groundwork for stem cell therapy, its translation to clinical practice has encountered significant challenges. The number of newly initiated phase I and II clinical trials experienced steady growth between 2006 and 2012 but has since shown signs of stagnation and decline as of 2018.[1-4,17,27] This trend can be attributed primarily to the underwhelming efficacy of stem cell therapy. The stark contrast between animal studies and patient outcomes is a key contributor to this disparity.[28,29] The goal of animal research is to reduce the number of experimental variables as much as possible, such as the animals' initial features and the precise location and severity of their injuries. But spinal cord injury patients are highly heterogeneous; they include differences in rehabilitation regimens, age, gender, comorbid problems, and the location and degree of the damage.[10,12,17,30,31] Consequently, the observed treatment efficacy in patients often falls markedly below that observed in animal models. Moreover, clinically recruited patients feature significant variations in their inclusion and exclusion criteria, coupled with disparities in injury location, severity, and timing. This diversity complicates the formation of a homogeneous patient cohort, even in well-designed randomized controlled trials, consequently clouding the interpretation of treatment efficacy and rendering it less precise and reliable.[27,30,32-34]

The advancements made in stem cell clinical trials have been nothing short of captivating. However, it's essential to note that the majority of these studies are still situated in the early phase I/II stages, with ongoing data collection.[17] At this juncture, confirming the substantial therapeutic impact of stem cells remains premature. Across various clinical trials, a multitude of disparities and uncertainties surface, spanning the selection of patients, types of cells utilized, timing of intervention, and the dosages and routes employed for stem cell transplantation.[35,36] This necessitates a closer synergy

between the preclinical and clinical dimensions of research. Improving trial safety, effectiveness, and repeatability; determining ideal transplant parameters; carefully weighing the advantages and disadvantages of stem cell treatment; and strengthening oversight practices in this area are among the urgent goals.[16,17]

CONCLUSION

Within the realm of SCI treatment, stem cell-based therapies exhibit substantial promise. While rodent models indisputably illustrate the efficacy of stem cells, our exhaustive analysis of clinical trials uncovers a paradox: despite the considerable potential of stem cells in improving neurological function among SCI patients, their transplantation carries the potential for numerous AEs. Ongoing clinical trials grapple with limitations, encompassing small sample sizes, subpar quality, and the absence of control groups, which collectively hinder the conclusive establishment of stem cell therapy's safety. It is, therefore, imperative to meticulously identify the optimal conditions and parameters for stem cell transplantation to optimize therapeutic outcomes.

Our findings highlight the lack of evidence currently available to justify the broad use of stem cell treatment for spinal cord injury and strongly advise against its immediate introduction into clinical practice. A deeper understanding of the pathophysiological mechanisms at play in SCI is imperative for the creation of treatments that surpass those presently in the investigative stage. Additionally, a range of concerns, encompassing ethical considerations and the assessment of tumorigenicity, immunogenicity, and immunotoxicity associated with diverse stem cell types, demand attention and resolution. The introduction of stem cell therapy into clinical practice should advance gradually and cautiously until well-structured animal experiments and high-caliber clinical studies are executed.

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