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Contents

Quarterly Volume 14 Number 1 March 18, 2024

EDITORIAL

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

World Journal of Transplantation

Quarterly Volume 14 Number 1 March 18, 2024

Contents

World Journal of Transplantation

Quarterly Volume 14 Number 1 March 18, 2024

Contents

ABOUT COVER

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WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, *etc.*

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SYSTEMATIC REVIEWS

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

Edoardo Agosti, Marco Zeppieri, Andrea Pagnoni, Marco Maria Fontanella, Alessandro Fiorindi, Tamara Ius, Pier Paolo Panciani

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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

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 American spinal injury association Impairment Scale (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.

Key Words: Spinal cord injury; Stem cell therapy; Adverse events; Functional outcomes; Systematic review

Core Tip: In the context of spinal cord injury (SCI) treatment, stem cell-based therapies exhibit promise, as demonstrated in this systematic review of 66 studies. However, the research reveals potential adverse events and limitations, emphasizing the importance of optimizing transplantation conditions, cautious clinical implementation, a deeper understanding of SCI pathophysiology, and addressing ethical, tumorigenicity, immunogenicity, and immunotoxicity concerns before a gradual and careful adoption of stem cell therapy in clinical practice. This underscores the need for further research to ensure the safety and effectiveness of these therapies for SCI patients, while acknowledging their potential for improving functional outcomes.

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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; and (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; and (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; and (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[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

Table 1 American Spinal Cord Injury Association Impairment Scale improvement scale

A = Complete	No sensory or motor function is preserved in the sacral segments S4–S5
B = Sensory incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch or pin-prick at S4–S5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body
C = Motor incomplete	Motor function is preserved below the neurological level AND more than half of the key muscle functions below the neurological level of injury have a muscle grade less than 3 (grades 0–2)
D = Motor incomplete	Motor function is preserved below the neurological level AND at least half (half or more) of the key muscle functions below the neurological level of injury have a muscle grade ≥ 3
E = Normal	If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments AND the patient has prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade

Time from injury: Immediate: 0-2 h after the injury; acute: Early acute phase: 2-48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 mo; chronic phase: > 6 mo.
AIS: American spinal injury association Impairment Scale; ISNCSCI: International Standards for Neurological Classification of SCI.

Modified Newcastle-Ottawa Quality Assessment Scale

Selection

(1) Representativeness of the exposed cohort
  (a) Consecutive eligible participants were selected, participants were randomly selected, or all participants were invited to participate from the source population,
  (b) Not satisfying requirements in part (a), or not stated.

(2) Selection of the non-exposed cohort
  (a) Selected from the same source population,
  (b) Selected from a different source population,
  (c) No description.

(3) Ascertainment of exposure
  (a) Medical record,
  (b) Structured interview,
  (c) No description.

(4) Demonstration that outcome of interest was not present at the start of the study
  (a) Yes,
  (b) No or not explicitly stated.

Comparability

(1) Were there clearly defined inclusion and exclusion criteria?
  (a) Yes,
  (b) No or not explicitly stated.

Outcome

(1) Assessment of outcome
  (a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records,
  (b) Record linkage (*e.g.*, identified through ICD codes on database records),
  (c) Self-report with no reference to original structured injury data or imaging,
  (d) No description.

(2) Was follow-up long enough for outcomes to occur?
  (a) Yes (≥ 12 months),
  (b) No (< 3 months).

(3) Adequacy of follow up
  (a) Complete follow up – all participants accounted for,
  (b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up or description provided of those lost),
  (c) Follow up rate < 85% and no description of those lost provided,
  (d) No statement.

Figure 1 Modified Newcastle-Ottawa Scale.

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.

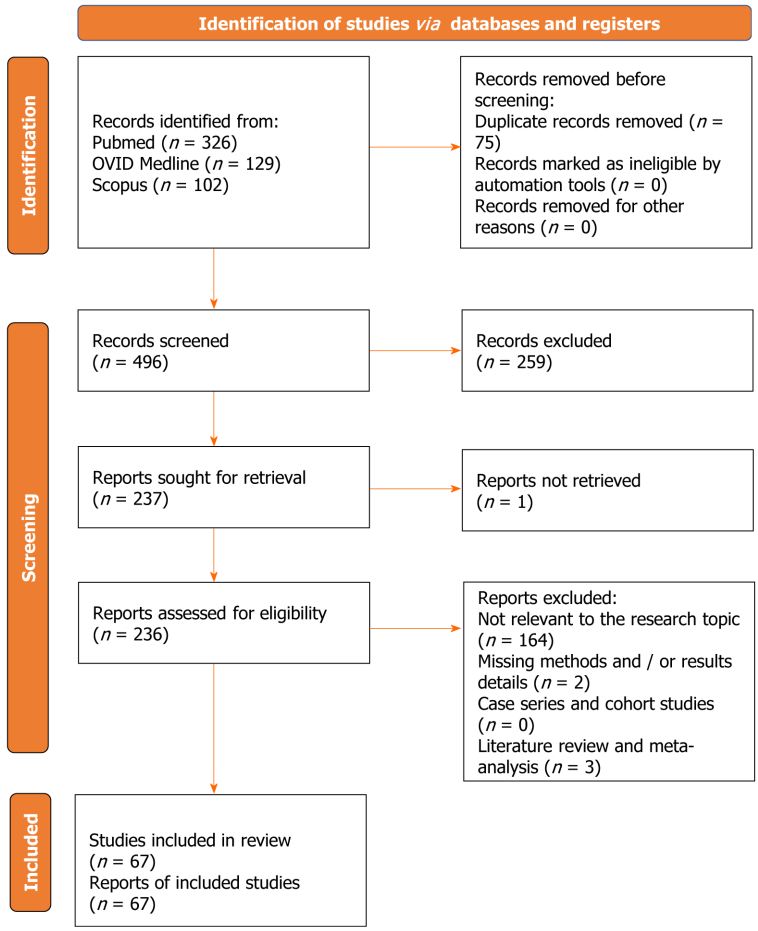

Figure 2 Flow chart according to the PRISMA statement.

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 mo. 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 2-6).

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].

Table 2 Summary of the studies included in the systematic literature review focusing on bone marrow derived stem cells (*i.e.*, BMSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from Injury		Functional improvement	Adverse effects
Park *et al*[37], 2005	N/A	6	Cervical	AIS A	Autologous (iliac bone marrow)	BMSC	1.98×10^{10}	Intralesional	N/A	6-18	AIS A→C 4, AIS A→B: 1, AIS A=A: 1	No serious adverse effects
Sykova *et al* [11], 2006	N/A	20	Cervical and thoracic	AIS A: 15; AIS B: 4; AIS C: 1	Autologous (iliac bone marrow)	BMSC	$104.0 \pm 55.3 \times 10^8$	Intravenous + Intraarterial	Subacute or chronic	24	AIS A→B: 1, AIS B→D: 1, AIS=: 15	No serious adverse effects
Chernykh *et al* [12], 2007	N/A	18	Cervical, Thoracic, Lumbar	N/A	Autologous (iliac bone marrow)	BMSC	N/A	Intralesional+ Intravenous	Chronic	9.4 ± 4.6	ASIA scale: significant increase in total sensitivity and motor activity score	No serious adverse effects
Yoon *et al* [13], 2007	I/II	35	Cervical (4) and thoracic (4)	N/A	Autologous iliac bone marrow	BMSC	1×10^8	Intralesional	Intermediate	10.4	AIS grade increased in 30.4% of the acute and subacute treated patients (AIS A→B or A→C)	No serious adverse effects
Geffner *et al* [14], 2008	N/A	8	Thoracic	AIS A: 5, AIS B: 1, AIS C: 2	Autologous iliac bone marrow	BMSC	1.2×10^6/kg	Intrathecal	4 acute and 4 chronic (average 114 months)	24	AIS A→C: 4, AIS B→C: 1, AIS C→D: 1 AIS =: 2	No serious adverse effects
Adel *et al*[38], 2009	N/A	43	Cervical and thoracic	AIS A: 40, AIS C: 3	Autologous iliac bone marrow	BMSC	$5\text{-}10 \times 10^6$	Intrathecal	Chronic (average 43.2 months)	6	AIS A→B: 11; AIS A→C: 1; AIS B→C: 3; AIS =: 28	ADEM: 1/43; Marked increased spasticity: 4/43; Neuropathic pain: 24/43
Kumar *et al* [39], 2009	I/II	297	N/A	AIS A: 249, AIS B: 12, AIS C: 34, AIS D: 2	Autologous iliac bone marrow	BMSC	N/A	Intrathecal	N/A	18.4-20.5	32.7% of the ASIA-classified patients showed improvement, in sensory and motor scale	No serious adverse effects. Mild-to-moderate neuropathic pain in few patients
Pal *et al*[40], 2009	N/A	30	Cervical and thoracic	AIS A: 24, AIS C: 6	Autologous iliac bone marrow	BMSC	1×10^6/kg	Intrathecal	< 6 months: 20, > 6 months: 30	12-36	No changes in the ASIA scale, SSEP, MEP and NCV	No serious adverse effects. Neuropathic pain in two patients
Abdelaziz *et al*[41], 2010	N/A	20	Thoracic	AIS A: 10, AIS B: 5, AIS C: 5	Autologous iliac bone marrow	BMSC	5×10^6/kg	Intrathecal + Intralesional	Chronic (> 6 months)	12	AIS A→B: 1, AIS A→C: 2, AIS B→C: 3; AIS=: 14	No serious adverse effects.Headache (12) and fever (3)
Bhanot *et al* [30], 2011	N/A	13	Cervical and thoracic	AIS A	Autologous	BMSC	$3\text{-}6\text{-}8 \times 10^6$/kg	Intrathecal	Intermediate and chronic (3-132 months, average 28)	6-38	AIS A→B: 1, Patchy improvement in sensations below the injured level: 2, Patient subjectively felt	No serious adverse effects. Transient increase in spasticity in the lower limbs (50%)

											improved sense of bladder filling: 1	
Park *et al*[35], 2012	N/A	10	Cervical	AIS A: 4, AIS B: 6	Autologous iliac bone marrow	BMSC	8×10^6 (intralesional) + 4×10^7 (subdural)	Intralesional + Subdural	> 1 months	6-62	Improvements in ADL, SSEP, MEP (3/10, all AIS B)	No serious adverse effects
Karamouzian *et al*[18], 2012	I/II	11	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	$0.7\text{-}1.2 \times 10^6$	Intrathecal	Acute and intermediate/chronic (max 1.5 months)	12-33	AIS A→C: 5, AIS=: 0	No serious adverse effects
Dai *et al*[28], 2013	N/A	20	Cervical	AIS A, ASIA score: 31.6 ± 9.82	Autologous iliac bone marrow	BMSC	2×10^7	Intralesional	Chronic (51.9 ± 18.3)	6	AIS A→B: 9, ASIA score: 43.1 ± 19.32	No serious adverse effects. Fever (2), Headache and dizziness (1), pain and numbness in spinal cord dominant area (2)
Jiang *et al*[19], 2013	N/A	20	Cervical (4), thoracic (11) and lumbar (5)	AIS A: 8, AIS B: 4, AIS C: 8	Autologous iliac bone marrow	BMSC	1×10^8	Intrathecal	Intermediate and chronic (3-120 months)	1	AIS A→B: 3, AIS A→C: 1, →AIS C→D: 8	No serious adverse effects. Fever and headache
Yazdani *et al*[42], 2013	I	8	Cervical (1) and thoracic (7)	AIS A	Autologous iliac bone marrow	BMSC	1×10^6	Intralesional	Chronic (13-63 months)	26-43	Although some improvement in light touch and pinprick sensation was observed, no improvement in ASIA classification was seen	No serious adverse effects
Amr *et al*[43], 2014	N/A	14	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	N/A	Scaffold	Intermediate and chronic (5-84 months, average 23 months)	24	AIS A→B: 2, AIS A→C: 12	Haematoma formation (2), Seroma formation (2)
Suzuki *et al*[44], 2014	N/A	10	Cervical and thoracic	AIS A: 5, AIS B:5	Autologous iliac bone marrow	BMSC	$2.03\text{-}8.44 \times 10^8$	Intrathecal	Intermediate and chronic (3 wk-12 months)	6	AIS A→B: 1, AIS B→C: 2, AIS B→D: 1; AIS=: 6	No serious adverse effects. Transient anemia after aspiration of bone-marrow cells (2)
Goni *et al*[45], 2014	N/A	9	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	N/A	Intrathecal	Chronic	24	No significant difference in the ASIA score. Statistically significant differences in the Functional Independence Measure and Modified Ashworth Scale	No serious adverse effects. Postoperative temporary neuropathic pain (2)
El-kheir *et al*[10], 2014	I/II	50	Cervical (10) and thoracic (40)	AIS A: 15, AIS B: 35	Autologous iliac bone marrow	BMSC	2×10^6/kg	Intrathecal	Chronic (12-36 months, average 18.3 ± 5)	18	AIS A→B: 12, AIS A→C: 4, AIS B→C: 18; AIS=: 16	Temporary mild side effects: Headache, neuropathic pain (30%). No long-term side effects
Mendonca *et*	I	14	Thoracic and	AIS A	Autologous	BMSC	5×10^6	Intralesional	Chronic (18-180	6	AIS A→B: 6, AIS A→C:	One subject developed a

al[46], 2014			lumbar		iliac bone marrow				months)		1; AIS=: 5; Improvements in urologic function (9) and changes in SSEP (1)	postoperatory complication, evolving a cerebrospinal fluid leak that was treated by an additional surgical procedure
Shin *et al*[47], 2015	I/IIa	19	Cervical	AIS A: 17, AIS B: 2	Human fetal brain	NSC	1×10^8	Intralesional	Acute and intermediate	12	AIS A→C: 2, AIS A→B: 1, AIS B→D: 2; AIS=: 14. Positive response in SSEP (35.3%) and MEP (58.8%) activities of AIS-A patients below the level of injury	No serious adverse effects
Chhabra *et al* [48], 2016	I/II	7	Thoracic	AIS A, ISCIS total score: 162.6 ± 3.1	Autologous iliac bone marrow	BMSC	3.6×10^8	Intrathecal	Acute	12	ISCIS total score: 134.9 ± 2.5	Liver abscess (1)
Oraee-Yazdani *et al* [49], 2016	I	6	Cervical (1) and thoracic (5)	AIS A	Autologous iliac bone marrow	BMSC	2×10^6	Intrathecal	Chronic (38.1 ± 15.3 months average)	25-36	AIS A→B: 1. Improvement in sensory level (2), improvement in UDS, especially bladder compliance (1)	No serious adverse effects
Oh *et al*[32], 2016	III	16	Cervical	AIS B	Autologous iliac bone marrow	BMSC	4.8×10^7	Subdural	Chronic (24-181 months)	6	SEP improvement (4), MEP improvement (6), improvement in motor grade (2)	No serious adverse effects. 8 patients developed mild adverse effects (muscle rigidity, worsened symptoms of tingling sense)
Thakkar *et al* [33], 2016	N/A	10	Thoracic and lumbar	AIS A	Autologous bone marrow + abdominal adipose tissue	BMSC	1.82×10^8	Intrathecal	Chronic (30-64.8 months)	34	AIS A→B: 6, AIS A→C: 3, AIS A→D: 1	No serious adverse effects
Vaquero *et al* [27], 2016	I/II	12	Thoracic	AIS A, ASIA score: 165.92 ± 22.83	Autologous bone marrow	BMSC	100×10^6 - 230×10^6	Intralesional	Chronic (38.0-321 months, average 166.3)	12	AIS→B: 3, AIS A→C: 1, ASIA score: 213.25 ± 37.19	22 adverse events of minor (79.1%) or moderate (20.9%) intensity.
Kakabadze *et al*[25], 2016	I	18	Cervical and thoracic	AIS A: 10, AIS B: 5, AIS C: 3	Autologous iliac bone marrow	BMSC	$405\text{-}964 \times 10^6$	Intrathecal	Intermediate and chronic (max 20 months)	12	ASIA scale improvement by one grade: 7/9 (78%) Improvement by two grades: 2/9 (22%)	No serious adverse effects. Transient fever and headache
Xiao *et al*[50], 2016	N/A	5	Cervical (1) and thoracic (4)	AIS A	Autologous iliac bone marrow	BMSC	1×10^9	Scaffold	Intermediate and chronic (max 32 months)	12	AIS A No improvement also in MEP and SSEP	No serious adverse effects.
Chhabra *et al* [51], 2017	I/II	7	Thoracic	AIS A, ISCIS total score: 172.2 ± 2.3	Autologous iliac bone marrow	BMSC	2×10^8	Intralesional	Acute	12	ISCIS total score: 141.7 ± 2.5	Liver abscess (1)

Vaquero *et al* [52], 2017	II	10	Cervical, thoracic and lumbar	AIS B: 5, AIS C: 5, ASIA total score: 118.2 ±60	Autologous	BMSC	30 × 10^6 × 4 doses	Intratechal	Chronic (29.2-415.1 months, mean 170.5 ± 118.6)	12	ASIA total score: 235.5 ± 49.35. Motor and sensory scores, bladder, bowel and sexual functions improved. Spasms (2) and neuropathic pain (2) improved	No serious adverse effects. Transient headache and pain in the area of the lumbar puncture
Larocca *et al* [21], 2017	I/II	5	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	2 × 10^7	Subcutaneous	Chronic (25-111 months)	6	AIS A→B: 1, AIS A=: 5; One patient improved AIS A→B but reversed at 6 months. Improvements in SCIM III and FIM scale scores	No serious adverse effects
Vaquero *et al* [20], 2018	II	11	Cervical (4), thoracic (4) and lumbar (3)	AIS A: 3, AIS B: 4, AIS C: 3, AIS D: 1	Autologous	BMSC	100 × 10^6 × 3 doses	Intrathecal	Chronic (mean 163.8 ± 177.5 months)	10	AIS improvement in 27% of patients. AIS A→B: 1, AIS B→C: 1; AIS C→D: 1	No serious adverse effects. Transitory sciatic pain (37.5%), headaches and pain in the area of lumbar puncture
Guadalajara *et al*[53], 2018	Case report	1	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	300 × 10^6 × 3 doses (1/months)	Intrathecal	Chronic	6	Improvement in functionality and especially in Krogh's; Neurogenic Bowel Dysfunction scale	No serious adverse effects
Srivastava *et al*[54], 2019	I	70	Thoracic and lumbar	AIS A	Autologous iliac bone marrow	BMSC	2,41 ± 1,198 × 10^6	Intrathecal	Acute and intermediate	12	AIS A→B: 21, AIS A→C: 29, AIS A→D: 5; AIS=: 15	No serious adverse effects
Phedy *et al* [55], 2019	Case report	1	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	10 − 17 × 10^6 (× 7 times)	Intrathecal ×1 + Intravenous ×6	Chronic	60	AIS A→C. Increase in AIS score: 10→30. Increase in MRC score for L1 and L2 innervated muscles: 0/5→3/5	No serious adverse effects
Chen *et al* [56], 2020	I	7	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	> 1 × 10^9	Scaffold	Acute or intermediate	36	All patients showed significant improvements in the FIM and ADL score. No obvious improvement in the ASIA grade, ASIA motor score, motor function, SSEPs, or MEPs was observed	Stress ulcer and lung infection (1), transient hyperthermia (1), shallow wound (1), spasm (4), paraplegic neuralgia (3), pressure ulcers (1), and lower limb amyotrophy (1)
Sharma *et al* [57], 2020	N/A	180	Cervical (63), thoracic and lumbar (117)	AIS A: 138, AIS B: 28, AIS C: 10, AIS D: 3	Autologous iliac bone marrow	BMSC	1.06 × 10^8	Intrathecal	Intermediate or chronic	2-16	FIM and WISCI showed statistically significant improvement	No serious adverse effects
Song *et al*[58], 2020	N/A	18	Cervical, thoracic and lumbar	ASIA score: 59.75 ± 5.22, SCIM-III score: 40.83 ±	Autologous iliac bone marrow	BMSC	1 × 10^7	Intrathecal	N/A	12	ASIA score: 81.1 ± 3.8, SCIM-III score: 72.5 ± 4.3	No serious adverse effects

				6.58								
Oraee-Yazdani *et al* [36], 2021	I/II	6	Cervical (1) and thoracic (5)	AIS A, SCIM III score: 28.9 ± 13	Autologous iliac bone marrow	BMSC	1×10^6	Intrathecal	Chronic (max 12 months)	30	SCIM III score: 43.1 ± 25.8. Sensory and/or motor improvement was evident in 9 patients according to the AIS assessment	Mild adverse effects: Increase in spasticity, numbness, or tingling sensation, and neuropathic pain
Honmou *et al* [59], 2021	II	13	Cervical	AIS A: 6, AIS B: 2, AIS C: 5	Autologous	BMSC (auto-serum expanded)	$84–150 \times 10^6$	Intravenous	Subacute	6	AIS A→B (3/6 patients), A→C (2/6), B→C (1/2), B→D (1/2), C→D (5/5)	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; ASIA: American Spinal Injury Association; BMSC: Bone Marrow Mesenchymal Stromal Cells; N/A: Not available; NSC: Neural stem cells.

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

Table 3 Summary of the studies included in the systematic literature review focusing on peripheral blood stem cells (*i.e.*, HSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from Injury		Functional improvement	Adverse effects
Deda *et al*[60], 2008	N/A	9	Cervical (6) and thoracic (3)	AIS A: 9	Autologous peripheral blood	HSC	5×10^6	Intrathecal	Chronic (6-51 months)	12	AIS A→B: 2, AIS A→C: 7	No serious adverse effects
Hammadi *et al* [61], 2012	N/A	277	Cervical (69) and thoracic (208)	N/A	Autologous peripheral blood	HSC	$1\text{-}8 \times 10^8$	Intrathecal	Chronic (6-104 months, average 34.5)	24	AIS A→B: 88, AIS A→C: 32, AIS = 157. A subgroup (12 patients) with lesion < 12 months had the best outcome: the percentage improvement reached 50%	No serious adverse effects. Backache and meningism (90%)
Al-Zoubi *et al* [62], 2014	N/A	19	Thoracic	AIS A	Autologous peripheral blood	HSC	7.6×10^7	Intrathecal	Chronic (12-48 months)	60	AIS A→B: 7. AIS A→C: 2, AIS =: 10	No serious adverse effects
Bryukhovetskiy *et al*[63], 2015	I/II	202	Cervical (98), thoracic (93) and lumbar (11)	N/A	Autologous peripheral blood	HSC	5.8×10^6	Intrathecal	Chronic (> 12 months)	144	Restoration of neurologic deficit (54.7%); Repair of the urinary system (47.7%). ASIA score improvement in 23 cases	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; HSC: Hematopoietic stem cells.

analysis revealed that only thirty percent of clinical trials sufficiently recorded different 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

Table 4 Summary of the studies included in the systematic literature review focusing on adipose tissue derived stem cells (*i.e.*, ADMSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from injury		Functional improvement	Adverse effects
Hur *et al*[26], 2016	I	14	Cervical (6), thoracic (7) and lumbar (1)	AIS A: 12, AIS B: 1, AIS D: 1	Autologous subcutaneous fat	ADMSC	9×10^7	Intrathecal	Intermediate and chronic (max 28 months)	8	Improvements in ASIA motor scores (5), voluntary anal contraction (2), ASIA sensory score (10), although degeneration was seen in 1. SSEP median nerve improvement (1)	No serious adverse effects. Transient headache, nausea and vomiting
Tien *et al*[64], 2019	N/A	31	Thoracic	AIS A, Barthel ADL: 3.35 ± 1.35	Autologous adipose tissue	ADMSC	$> 1 \times 10^8$	Intrathecal	Acute	12	AIS A→B: 10, AIS A→C: 1, AIS A→D: 2; AIS =: 16 Barthel ADL: 6.48 ± 2.14	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. ADL: Activities of Daily Living; ADMSC: Adipose-derived mesenchymal stem cells; AIS: American spinal injury association Impairment Scale.

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.

Table 5 Summary of the studies included in the systematic literature review focusing on nervous tissue derived stem cells (*i.e.*, NSC, huCNSSC, OEC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from injury		Functional improvement	Adverse effects
Shin *et al*[47], 2015	I/IIa	19	Cervical	AIS A: 17, AIS B: 2	Human fetal brain	NSC	1×10^8	Intralesional	Acute and intermediate	12	AIS A→C: 2, AIS A→B: 1, AIS B→D: 2; AIS=: 14. Positive response in SSEP (35.3%) and MEP (58.8%) activities of AIS-A patients below the level of injury	No serious adverse effects
Ghobrial *et al* [65], 2017	II	5	Cervical	AIS A: 1, AIS B: 4	Allogeneic fetus	huCNSSC®	$15\text{-}40 \times 10^6$	Intrathecal	Chronic	12	AIS A→B: 1, AIS B→A: 1, AIS=: 3, GRASSP score mean improvement: 14.8 ± 7.8, ISNCSCI score mean improvement: 17.3 ± 16.8	No serious adverse effects
Anderson *et al* [66], 2017	I	6	Thoracic	N/A	Autologous (sural nerve)	SC	$5, 10 \text{ or } 15 \times 10^6$	Intramedullary	Subacute	12	AIS A→B: 1. Improvement in FIM and SCIM III scores	No serious adverse effects
Levi *et al*[67], 2018	I/II	29	Cervical: 17 (Cohort I: 6, Cohort II: 11) Thoracic: 12	AIS A: 11, AIS B: 18	Allogeneic (Stemcells Inc.)	huCNSSC®	$15 - 40 \times 10^6$	Intramedullary	Subacute	Up to 56	Improvement in AIS motor scores	15 serious adverse effects in cervical group and 4 in thoracic
Curtis *et al*[68], 2018	I	4	Thoracic	AIS A	Allogeneic (human-spinal-cord-derived neural stem cell)	NSI-566®	6 injections (Mean number)	Intramedullary	Chronic	60	Improved AIS scores, neurological levels and EMG findings. No improvement in QoL	No serious adverse effects
Levi *et al*[69],	I/II	17 Cohort I: 6,	Cervical	AIS A, B	Allogeneic	huCNSSC®	15 + 30 + 40 ×	Intramedullary	Intermediate or	12	Improvement	No serious

2019		Cohort II: 11 6/11 monitored			(Stemcells Inc.)		10^6 (Coh.I) 40 × 10^6 (Coh.II)		Chronic (max 24 months)		in UEMS score	adverse effects
Curt *et al*[70], 2020	I/IIa	12	Thoracic	AIS A: 7, AIS B: 5	Allogeneic (Stemcells Inc.)	huCNSSC®	20×10^6	Intramedullary	Intermediate or chronic (max 24 months)	72	Sensory improvements in 5 out of 12 patients. No motor improvements were observed	N No serious adverse effects
Zamani *et al* [71], 2021	I	3	Thoracic	AIS A	Autologous	OEC+ BMSC	15×10^6, OEC/BMSC = 1/1	Intrathecal	Chronic	24	AIS A→B: 1 and 6 points improvement in SCIM	Mild adverse effects
Gant *et al*[72], 2022	I	8	Cervical: 4; Thoracic: 4	N/A	Autologous (sural nerve)	SC	$50 - 200 \times 10^6$	Intramedullary	Chronic	60	The neurological level improved by 1 level in 1 patient. Improvement in Sensory score in all patients with thoracic and in 2 patients with cervical lesion	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; BMSC: Bone Marrow Mesenchymal Stromal Cells; EMG: Electromyography; MSC; Mesenchimal stem cell; NSC: Neural stem cells; OEC: Olfactory ensheathing cell; SC: Stem cell; SCIM: Spinal cord independence measure.

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].

Table 6 Summary of the studies included in the systematic literature review focusing on nervous tissue derived stem cells (*i.e.*, UCMSC, HUCBC, HESC, WJ-MSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from injury		Functional improvement	Adverse effects
Dai *et al*[29], 2013	N/A	18	Cervical and thoracic	AIS A: 12, AIS B: 4, AIS C: 2	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^7	Intralesional	Chronic (18.67 ± 7.6 months)	6	AIS A→B: 7, AIS B→C: 3, AIS=: 8; MEP improvements	No serious adverse effects
Liu *et al*[73], 2013	N/A	22	Cervical (4), cervical + thoracic (2), thoracic + lumbar (2) and lumbar (7)	Motor function: 58.1 ± 22.2. Algesia: 73.2 ± 25.1. Sensory function: 74.2 ± 26.7. ADL: 29.5 ± 12.5	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^6/kg	Intrathecal	Intermediate and chronic (2-204 months)	> 12	Motor function: 61.5 ± 23.9. Algesia: 77.2 ± 26.1. Sensory function: 77.3 ± 26.1. ADL: 32.7 ± 12.4	Fever, lumbago, headache, dizziness and other adverse reactions were observed
Cheng *et al*[74], 2014	N/A	10	Thoracic and lumbar	AIS A, Barthel Index: 33.50 ± 6.69	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^7	Intralesional	Chronic (12-72 months)	6	Barthel Index: 41.40 ± 6.42; Muscle strength increased. Muscle tension decreased. Increase in maximum bladder capacity and decrease in maximum detrusor pressure	No serious adverse effects
Shroff *et al*[34], 2016	N/A	226	Cervical and thoracic	AIS A: 153, AIS B: 32, AIS C: 36, AIS D: 5	Pre-implantation stage fertilized ovum	HESC	1.6×10^7 + 1-5 × 1.6×10^7	Intravenous + intralesional	Intermediate and chronic	6-18	AIS A: 98, AIS B: 67, AIS C: 126, AIS D: 9, AIS E: 3	No serious adverse effects. Transient fever and headache
Shroff *et al*[75], 2017	N/A	15	Cervical and thoracic	AIS A: 13, AIS B: 2	Pre-implantation stage fertilized ovum taken during natural IVF process	HESC	1.6×10^7 + 1-5 × $1,6 \times 10^7$	Intravenous + intralesional	Acute, intermediate and chronic (6-15 months)	9	AIS A: 10, AIS B: 2, AIS C: 3	No serious adverse effects
Zhao *et al*[76], 2017	N/A	8	Cervical (4) and thoracic (4)	AIS A	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^7	Scaffold	Intermediate and chronic (max 36 months)	12	Expansion of sensation level (62.5%) and expansion of the MEP-responsive area	No serious adverse effects

											(87.5%) but AIS=	
Xiao *et al*[77], 2018	I	2	Cervical and thoracic	AIS A	Allogeneic	UCMSC+ Scaffold	40×10^6	Intramedullary	Acute	12	AIS A→C in both patients	No serious adverse effects
Deng *et al*[72], 2020	I	20	Cervical	AIS A	Allogeneic	UCMSC+ Scaffold	40×10^6 (Collagen scaffold)	Intramedullary	Acute	12	AIS A→B (9 patients), AIS A→C (2 patients). Improvement in ADL scores. Improvement in bowel and bladder function	No serious adverse effects
Albu *et al*[31], 2021	I/IIa	10	Thoracic	AIS A	Allogeneic	WJ-MSC	10×10^6	Intrathecal	Chronic	6	Significant improvement in pinprick sensation in compared with placebo group. No changes in motor function, independence, QoL, SEPs, MEPs, spasticity or bowel function	No serious adverse effects
Yang *et al*[23], 2021	I/II	102	Cervical, thoracic and lumbar	ASIA score: 158.15 ± 70.93, IANR-SCIFRS total score: 24.54 ± 9.82	Allogeneic neonatal umbilical cord tissue	UCMSC	1×10^6/kg	Intrathecal	Intermediate and chronic (max 240 months)	12	ASIA score: 183.88 ± 69.76, IANR-SCIFRS total score: 29.49 ± 10.47	No serious adverse effects. Fever (14.1%), headache (4.2%), transient increase in muscle tension (1.6%) and dizziness (1.3%)
Zhao *et al*[78], 2021	N/A	7	Cervical (3) and thoracic (4)	ASIA pin prick: 55.00 ± 28.46, ASIA light touch: 55.00 ± 28.46, ASIA motor score: 42.00 ± 28.19	Allogeneic neonatal umbilical cord tissue	UCMSC	5×10^4	Intrathecal	Intermediate and chronic (max 60 months)	6	ASIA pin prick: 57.06 ± 30.01, ASIA light touch: 58.20 ± 29.36, ASIA motor score: 44.13±27.23	No serious adverse effects
Smirnov *et al* [16], 2022	I/IIa	10	Cervical, thoracic and lumbar	AIS A: 6, AIS B: 4	Allogeneic	HUCBC	14.8×10^6/kg (Total cell number for 4 infusions)	Intravenous	Acute	12	AIS A→C: 3, AIS B→D: 2, AIS B→E: 2, AIS A→D: 1	No serious adverse effects related to therapy

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; HESC: Human embryonic stem cells; HUCBC: human umbilical cord blood mononuclear cells; UCMSC: Umbilical cord derived mesenchymal stem cells; WJ-MSC: Wharton's jelly-Mesenchymal stem cells.

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.

ARTICLE HIGHLIGHTS

Research 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.

Research motivation

Current research primarily emphasizes safety in early-phase clinical trials, while systematic reviews prioritize effectiveness, often overlooking safety and translational feasibility.

Research objectives

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

Research methods

A systematic search was conducted across major medical databases.

Research 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.

Research conclusions

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.

Research perspectives

There is a need for further research to ensure the safety and effectiveness of these therapies for SCI patients, while acknowledging their potential for improving functional outcomes.

FOOTNOTES

Author contributions: Agosti E wrote the outline, did the research, wrote the paper, and provided the final approval of the version of the article; Zeppieri M assisted in the conception and design of the study, writing, outline, final approval of the version of the article to be published and completed the English and scientific editing; Maria M Fontanella assisted in the editing and making critical revisions of the manuscript; Alessandro F assisted in the writing, editing and making critical revisions of the manuscript; Tamara Ius assisted in the writing, editing and making critical revisions of the manuscript; Panciani PP assisted in the writing, editing and making critical revisions of the manuscript.

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