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Clinical efficacy of bone marrow mesenchymal stem cells in chronic spinal cord injury: A single-arm meta-analysis of clinical trials

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ABSTRACT

Background: Chronic spinal cord injury (SCI) leads to irreversible neurological deficits with limited therapeutic options, making it a major challenge in neuroregenerative medicine. This study aimed to evaluate the clinical efficacy of bone marrow mesenchymal stem cells (BMMSC) therapy in patients with chronic SCI using a single-arm meta-analysis.

Methods: This research was conducted using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, covering studies up to August 2024 in PubMed, CENTRAL, and ScienceDirect. Included trials applied BMMSC therapy in patients ≥1 year post-injury. A random-effects model was employed using R software. Outcomes included changes in the American Spinal Injury Association (ASIA) impairment scale, somatosensory evoked potentials (SSEP), motor evoked potentials (MEP), infralesional voluntary muscle contraction (IVMC), active muscle reinnervation (AMR), and urodynamic parameters. Heterogeneity was assessed with the I^2 statistic, and study quality was evaluated via ROBINS-I. This study has been registered on PROSPERO with registration number CRD42024577161.

Results: Seven studies comprising 133 patients were included. AIS grade improvement was observed in 0.37 (95% CI: 0.24–0.52). Improvements were also seen in SSEP at 0.40 (95% CI: 0.18–0.67), MEP at 0.37 (95% CI: 0.25–0.51), IVMC at 0.47 (95% CI: 0.34–0.60), and AMR at 0.74 (95% CI: 0.39–0.92). Urodynamic outcomes demonstrated increased maximum cystometric capacity [0.48 (95% CI: 0.30–0.67)], improved bladder compliance [0.73 (95% CI: 0.55–0.85)], and reduced detrusor pressure [0.61 (95% CI: 0.43–0.76)].

Conclusion: BMMSC therapy was associated with clinically meaningful neurological and urodynamic improvements in chronic SCI. Standardized administration protocols and randomized controlled trials are necessary to validate efficacy and optimize treatment paradigms.

Keywords: bone marrow mesenchymal stem cells, chronic spinal cord injury, neurological recovery, urodynamic function.
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INTRODUCTION

Chronic spinal cord injury (SCI) remains one of the most challenging conditions in clinical medicine, marked by irreversible neurological deficits originating from the restricted regenerative potential of the central nervous system (CNS). SCI typically results in severe, lifelong impairments of motor, sensory, and autonomic functions, significantly reducing the quality of life for affected patients and creating substantial socioeconomic challenges.[1,2] Existing therapeutic approaches, including surgical decompression, pharmacological interventions, and intensive rehabilitation, frequently result in suboptimal functional recovery, underscoring the urgent necessity for innovative and effective treatment strategies.[3,4]

Recent advances in regenerative medicine have positioned stem cell therapy as a promising therapeutic strategy, targeting the secondary pathological processes associated with spinal cord injury, such as neuroinflammation, demyelination, and gliosis.[2,5] Bone marrow mesenchymal stem cells (BMMSC) stand out among the diverse variations of stem cell types, primarily because of their significant regenerative potential, immunomodulatory characteristics, and the relative simplicity involved in their collection and expansion.[6,7] BMMSCs demonstrate significant neuroprotective capabilities through the secretion of trophic factors, modulation of inflammatory responses, enhancement of remyelination, and support of axonal regeneration, positioning them as a highly pertinent candidate for the treatment of chronic SCI pathology.[8]

Because of these favorable characteristics, the clinical application of BMMSC therapy in spinal cord injury continues to be a subject of debate, primarily due to the variability in outcomes observed across various clinical trials. The

differences in methodological approaches, including cell isolation techniques, dosage, timing of administration, and route of delivery, have played a crucial role in the inconsistencies observed in reported outcomes.[4,9] For example, a study demonstrated that intramedullary transplantation of human neural stem cells, which share a close relationship with BMMSCs, is both feasible and safe. However, the enhancements in functional outcomes were limited and exhibited significant variability among participants.[4] In the same way, other studies revealed inconsistent clinical outcomes concerning enhancements in motor and sensory functions, highlighting the lack of consensus and the absence of a robust quantitative synthesis of therapeutic outcomes.[3,7]

Another essential component of chronic spinal cord injury treatment involves evaluating advancements that extend beyond mere motor recovery, encompassing electrophysiological metrics and urodynamic functionality. Recent findings indicate that BMMSC transplantation may markedly improve neurophysiological indicators, including somatosensory evoked potentials (SSEP), motor evoked potentials (MEP), and active muscle reinnervation. These enhancements suggest a promising avenue for functional restoration at the neural circuit level.[7,10] Furthermore, research has indicated substantial advancements in bladder functionality, characterized by marked increases in maximum cystometric capacity, enhanced bladder compliance, and diminished detrusor pressure. These factors collectively contribute to an improved quality of life for patients by mitigating secondary complications linked to neurogenic bladder dysfunction.[11]

Despite these encouraging findings, no meta-analysis to date has systematically synthesized single-arm clinical trial data to quantify the true therapeutic efficacy of BMMSC transplantation in chronic SCI. This represents a critical evidence gap, as most prior studies have been underpowered, heterogeneous, or descriptive in nature. Considering the ethical and logistical constraints of conducting placebo-controlled randomized trials in chronic SCI, a single-arm meta-analysis offers a practical and reliable methodology for consolidating outcomes across existing clinical studies.

Therefore, this study was designed to determine whether bone marrow mesenchymal stem cell transplantation leads to measurable improvements in neurological, electrophysiological, and urodynamic outcomes in patients with chronic spinal cord injury. By systematically synthesizing available clinical trial data, we aim to provide the most comprehensive quantitative evaluation of BMMSC efficacy in chronic SCI to date, thereby clarifying therapeutic potential and informing the development of standardized regenerative treatment strategies.

METHODS

Eligibility Criteria

This systematic review and single-arm meta-analysis implemented specified eligibility requirements to guarantee methodological rigor, clinical relevance, and interpretability of pooled results. Studies were considered suitable if they were original, peer-reviewed clinical trial studies involving human patients with a confirmed diagnosis of traumatic chronic SCI who were treated with bone marrow-derived mesenchymal stem cells. Only clinical trials were included because they provide higher methodological quality, structured intervention protocols, and systematically measured outcomes compared with case reports, case series, or observational studies. This restriction was intended to minimize heterogeneity from poorly standardized designs, ensure that treatment effects were based on prospectively collected data, and enhance the internal validity of pooled estimates.

The term chronic was operationally defined as a post-injury duration of at least 10 months, indicating that subjects were in the stable, post-acute phase of damage, where spontaneous healing is physiologically restricted. Only studies with quantified pre- and post-treatment results such as (1) neurological outcomes, such as association impairment scale (AIS) grade changes in motor or sensory scores; (2) electrophysiological outcomes, such as changes in SSEP, MEP, infralesional voluntary muscle contraction (IVMC), and active muscle reinnervation (AMR); or (3) urodynamic outcomes, which included detrusor pressure, bladder compliance, and maximum cystometric capacity, were included.

Participants had to be between the ages of 16 and 65, have chronic SCI in the cervical, thoracic, or lumbar spinal segments, and have a baseline American Spinal Injury Association (ASIA) impairment scale grade of A to D, indicating complete or near-complete loss of function below the level of the injury. To avoid confounding the source of therapeutic effect, eligible studies were required to administer only BMMSCs, either autologous or allogeneic, without combining them with other cell-based therapies (e.g., olfactory ensheathing cells, Schwann cells) or investigational neuropharmacological agents.

Studies were excluded if they did not provide full text in English, had no clear definition of injury chronicity, featured non-traumatic etiologies such as transverse myelitis or demyelinating illnesses, or failed to describe the origin and kind of stem cells employed. Other exclusion criteria included studies enrolling patients with anatomical spinal cord transection, penetrating injuries, as well as the presence of serious systemic illnesses such as hepatic or renal dysfunction, active infections (e.g., pneumonia or urinary tract infection), autoimmune disorders, hematological malignancies, or seropositivity for hepatitis B, hepatitis C, HIV, or syphilis.

Information Sources and Search Strategy

A thorough literature search was performed from three high-impact biological databases, such as PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and ScienceDirect, from August 2024 to January 2025. These databases were chosen because of their broad indexing of clinical trials and good retrieval specificity in neurosurgery, regenerative medicine, and spinal trauma.

To provide the highest sensitivity and specificity, the search technique included both restricted vocabulary and free-text phrases. Medical subject headings (MeSH) and equivalent index

terms included "*Mesenchymal Stem Cells*," "*Bone Marrow Mesenchymal Stem Cells*," "*Spinal Cord Injuries*," "*Chronic Disease*," "*Cell- and Tissue-Based Therapy*," "*Neurological Recovery*," "*Motor Function*," "*Somatosensory Evoked Potentials*," "*Motor Evoked Potentials*," "*Electrophysiological Phenomena*," "*Bladder Function*," and "*Urodynamics*." These were coupled with Boolean operators ("AND," "OR") to compose the query logic appropriately.

Selection Process

All records obtained from electronic databases and registries were integrated into reference management software for deduplication. Following the elimination of duplicates, two reviewers independently reviewed the titles and abstracts of all unique entries based on predetermined eligibility criteria. Potentially relevant studies were retrieved in full text and evaluated for final inclusion. The same two reviewers evaluated full-text publications simultaneously, with disagreements resolved through discussion or consultation with a third senior reviewer to ensure consensus and methodological consistency.

Each study was assessed based on its adherence to the inclusion and exclusion criteria, with a focus on participant eligibility, intervention specificity BMMSC, injury chronicity, and outcome reporting. The whole selection process, including reasons for study exclusion at the full-text stage, is recorded in a preferred reporting items for systematic reviews and meta-analyses (PRISMA)-compliant flow diagram to guarantee transparency and repeatability of the screening approach.

Data Extraction Process

Data extraction was carried out utilizing a standardized computerized data collecting form that was intended to assure uniformity and reduce extraction bias. Two independent reviewers extracted relevant information from each eligible study, including study design, sample size, demographic characteristics, injury level and chronicity, ASIA impairment scale, BMMSC intervention details (source, dose, delivery route, number of administrations), follow-up duration, and all reported clinical outcomes. To aid structured synthesis, these results were organized into neurological, electrophysiological, and urodynamic domains.

The data extraction process was performed in duplicate, with any discrepancies between reviewers resolved through discussion. In cases where data were incomplete, unclear, or inconsistently reported, the corresponding authors were contacted to request additional information or clarification. If authors did not respond or if data could not be obtained, only clearly interpretable and verifiable results were included in the analysis. No automated techniques were employed in the data-gathering process. Therefore, all data points were manually validated for correctness, completeness, and compatibility with the inclusion criteria.

Data Items

The primary outcome was the proportion of patients who showed an improvement in their AIS grade from baseline after receiving BMMSC. AIS grade changes are commonly considered as clinically important indications of neurological rehabilitation, as they include both sensory and motor functions.

Secondary outcomes focused on neurophysiological and urodynamic measures to provide a detailed assessment of functional restoration. Neurophysiological outcomes were assessed using SSEP to evaluate ascending sensory pathways, MEP to assess corticospinal conduction, IVMC to identify retained or restored voluntary motor control below the lesion, and AMR to measure recovery at the neuromuscular junction. Urodynamic outcomes were assessed using maximum cystometric capacity (MCC) to determine bladder storage capacity, bladder compliance to evaluate bladder expansion without increased pressure, and detrusor pressure during the filling phase to assess autonomic control of bladder function.

Comprehensive study-level variables were also retrieved to contextualize the treatment impact. These included the nation and year of publication, total number of participants, research phase and design, and inclusion criteria, such as the AIS classification and injury chronicity. Intervention-related characteristics were systematically documented, including the route of BMMSC administration (e.g., intraspinal, intramedullary, intrathecal, or subarachnoid), dosage and volume, frequency and number of administrations, and biological formulation (e.g., expanded cells in autologous plasma). Patient demographics, including age range, mean age ± standard deviation, and time from SCI start to intervention, were also documented. Only data expressly stated in the original publications or validated through author communication were used.

Risk of Bias Assessment

The risk of bias in non-randomized studies - of interventions (ROBINS-I) tool was used to assess the methodological quality and internal validity of the included clinical trials, which is recommended for non-randomized designs. This tool evaluates possible sources of bias in seven domains: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and reported result selection. To reduce subjectivity, each domain was separately reviewed by two reviewers, with any disagreements handled by discussion with the third reviewer. The assessment was conducted at the study level, with judgments categorized as low, moderate, serious, or critical risk of bias per ROBINS-I guidance. There were no automated tools or machine learning algorithms employed in this approach. Thus, clinical and contextual judgment remained crucial to bias evaluation. Sensitivity analyses were planned by excluding studies at moderate risk of bias to evaluate the robustness of pooled estimates.

Effect Measures and Synthesis Method

This meta-analysis used pooled proportions to assess the therapeutic effectiveness of BMMSC treatment in patients with chronic SCI. Dichotomous outcomes from each trial were retrieved and synthesized, with an emphasis on neurological progress (AIS grade), electrophysiological responses (SSEP, MEP, IVMC, AMR), and urodynamic markers (MCC, bladder compliance,

detrusor pressure). Effect sizes were determined using proportions and 95% confidence intervals (CIs). A random-effects model with the inverse variance approach was used to account for between-study variability caused by changes in research design, patient characteristics, delivery methods, and dosing procedures.

The heterogeneity was measured using the I^2 statistic and τ^2 values. Separate meta-analyses were performed for each outcome domain, and the findings were shown using forest plots to aid in the comprehension of individual and pooled estimates. All statistical analyses were carried out using R software (version 4.0.2) and the "*meta*" and "*metaprop*" packages.

Pre-specified subgroup analyses (e.g., stratified by route of BMMSC administration: intramedullary, intrathecal, intraspinal, or subarachnoid) were planned and conducted only when sufficient studies reported comparable data. Moreover, publication bias was assessed, when at least 10 studies were available per outcome, using funnel plots and Egger's regression test.

RESULTS

Study Selection

The initial systematic search of PubMed, CENTRAL, and ScienceDirect produced a total of 4,725 entries (PubMed: 521; Cochrane: 55; ScienceDirect: 4,176). After removing 385 duplicate data and excluding 3,873 items judged irrelevant based on title and abstract screening, 467 records were kept for further assessment. Upon careful analysis, 62 full-text reports were identified for retrieval. Of these, 16 publications were inaccessible, leaving just 25 papers for comprehensive eligibility evaluation. Among the inaccessible studies, the primary reasons were reports not available online despite indexed citations, full text available only in the local language without an English translation, and conference abstracts without subsequent peer-reviewed publication.

After a thorough full-text screening, 18 papers were rejected for the following reasons: out-of-scope topics (n=4), use of alternative stem cell types (n=4), failure to fulfill the chronicity criteria for spinal cord injury (n=7), and unavailability of complete texts despite retrieval attempts (n=3). Finally, seven clinical studies satisfied all of the inclusion criteria and were included in the meta-analysis. The PRISMA 2020 flow diagram (Figure 1) clearly summarizes the selection process by outlining the steps of identification, screening, and inclusion.

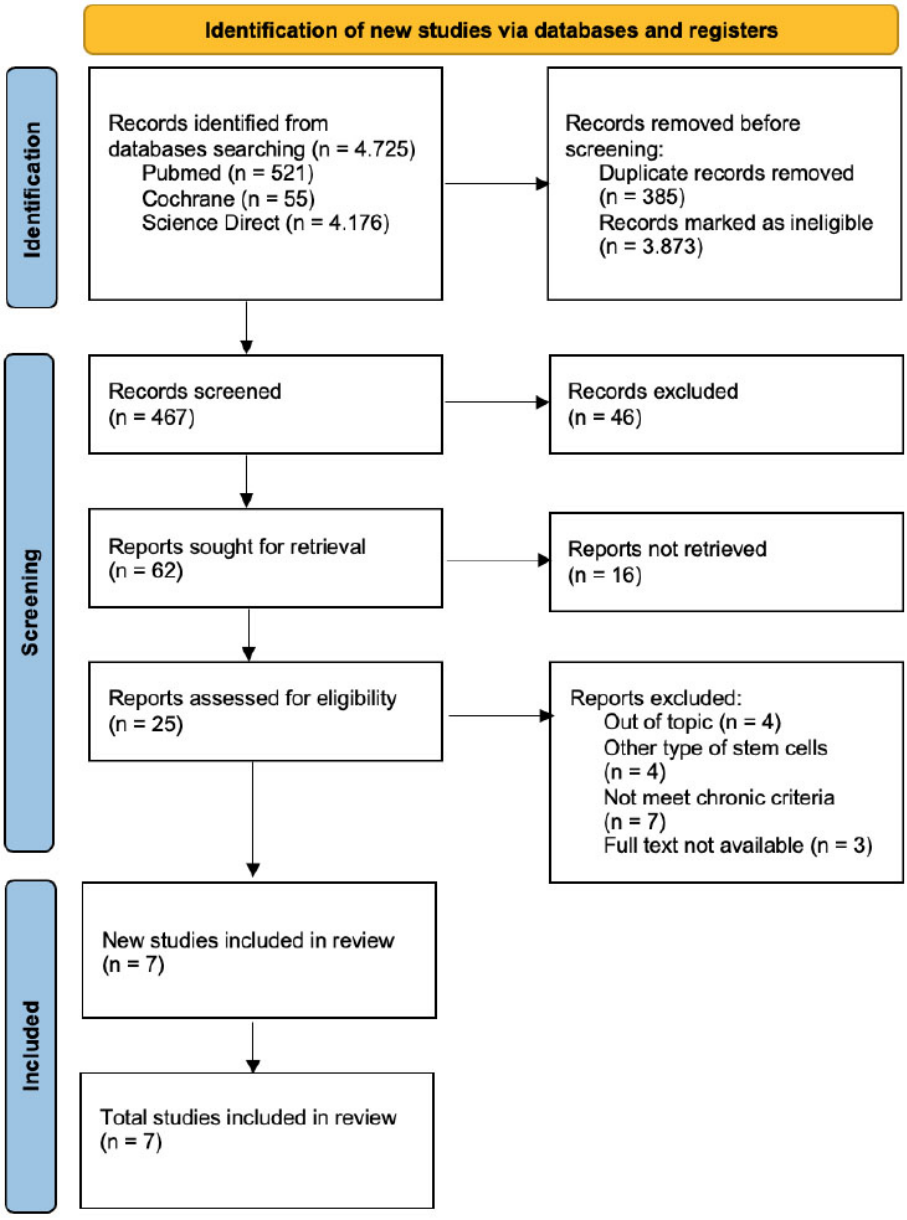

Figure 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) algorithm of the study.

Study Characteristics

A total of seven clinical trials comprising 133 participants with chronic SCI were included in this meta-analysis. All chosen studies used autologous BMMSCs as the therapeutic intervention, which ensured immunocompatibility and reduced the risk of graft rejection or unfavorable immunological reactions. The studies were carried out in a variety of geographic locations, including China, Egypt, Brazil, Korea, and Spain, demonstrating a widespread international interest in the regenerative potential of BMMSCs for SCI.

As shown in Table 1, the research designs varied from Phase I to Phase III clinical trials, with the majority being classed as early-phase (I/II) studies. The number of participants per research ranged between 10 and 50, with the majority of studies recruiting less than 20 patients.

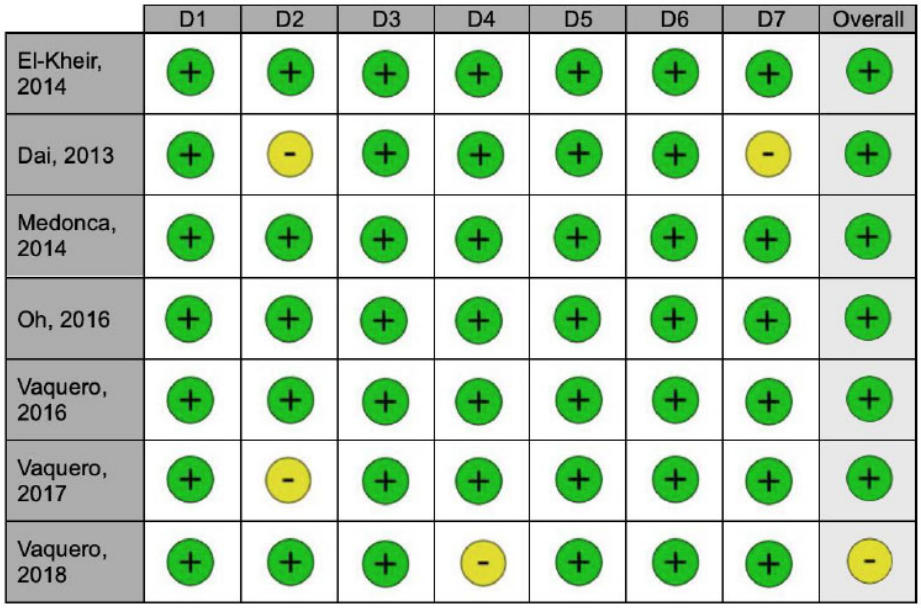

Figure 2. Risk of bias in non-randomised studies – of interventions (ROBINS-I) assessment of included studies.

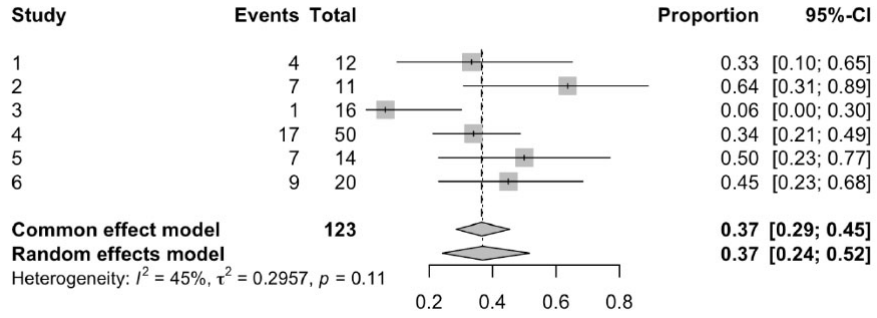

Figure 3. Forest plot of the association impairment scale (AIS) improvement outcome.

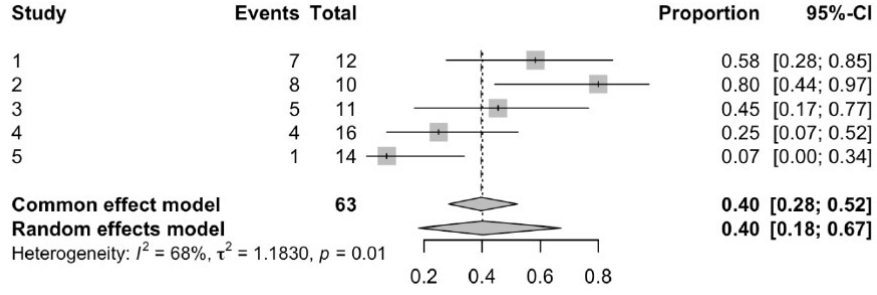

Figure 4. Forest plot of the somatosensory evoked potentials (SSEP) outcome.

The inclusion criteria were reasonably constant, with an emphasis on individuals with traumatic SCI categorized as AIS grade A or B. Moreover, two clinical trials expanded eligibility to include AIS grade D individuals. The time from injury to intervention ranged from 1.5 months to 74 months, while most investigations focused on chronic patients, with typical durations well over a year. Follow-up periods varied from six to eighteen months, allowing enough time to assess both safety and preliminary effectiveness results.

Table 2 summarizes the intervention protocols. The administration routes varied between trials, including intraspinal, intramedullary, subarachnoid, and intrathecal injections. Dosage and injection sizes varied greatly, from small-scale microinjections (e.g., 25 µL at 8 × 10^5 cells/µL) to high-dose regimens delivering up to 300 × 10^6 MSCs throughout numerous sessions. This variety reflects continuing research to enhance delivery tactics and dosage paradigms based on spinal lesion characteristics and patient profiles.

Risk of Bias in Studies

The methodological quality evaluated using the ROBINS-I tool were seen in Figure 2. Most studies had a consistently low risk of bias across all domains, as shown by green markers. This demonstrates a general high adherence to clinical trial standards, particularly in domains such as intervention integrity, outcome monitoring, and reporting transparency. Three studies showed a moderate risk of bias (as shown by yellow markers) in specified domains. However, none of these limitations were thought to significantly compromise the general validity of the findings. As a result, six of the seven trials were graded as having a low overall risk of bias, with only one research being classified as having a moderate overall risk.

Primary Outcome: AIS Improvement

Analysis from six clinical studies including 123 participants revealed that 37% of patients showed at least one-grade improvement in AIS classification after intervention (proportion: 0.37; 95% CI: 0.24-0.52), as seen in the forest plot (Figure 3). The analysis used a random-effects model to account for inter-study variability, resulting in a relatively small heterogeneity index (I^2 = 45%, τ^2 = 0.2957, p = 0.11). This suggests a clinically meaningful subset of chronic SCI patients demonstrated neurological recovery following BMMSC therapy.

Neurophysiological Evaluations Outcome: SSEP

Analysis from five clinical studies comprising a total of 63 participants demonstrated that 40% of patients exhibited improvements in SSEP following BMMSC administration (proportion: 0.40; 95% CI: 0.18–0.67), as illustrated in

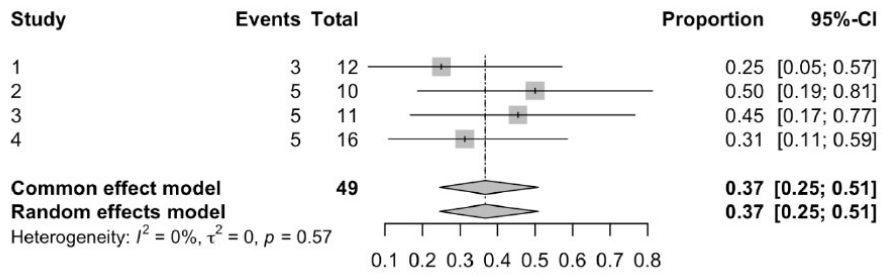

Figure 5. Forest plot of the motor evoked potentials (MEP) outcome.

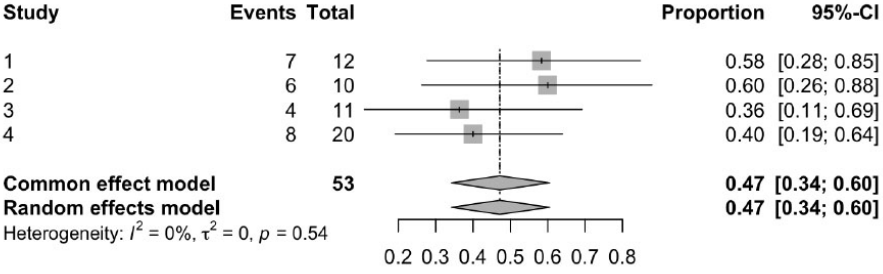

Figure 6. Forest plot of the infralesional voluntary muscle contraction (IVMC) outcome.

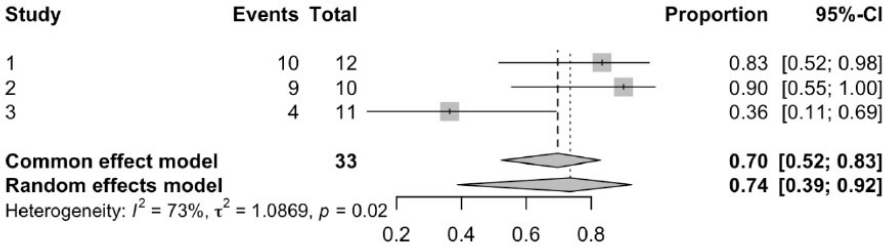

Figure 7. Forest plot of the active muscle reinnervation (AMR) outcome.

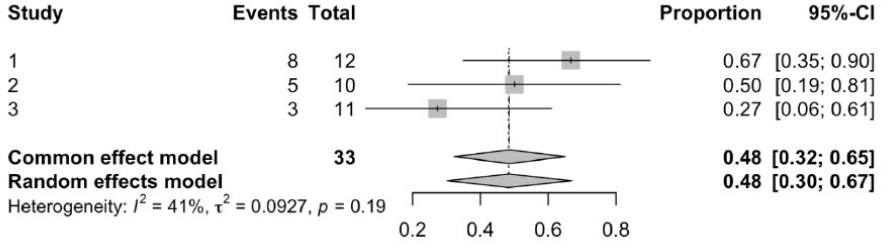

Figure 8. Forest plot of the maximum cystometric capacity (MCC) outcome.

the forest plot (Figure 4). The analysis was conducted using a random-effects model to accommodate potential inter-study heterogeneity, which yielded a moderate heterogeneity index (I^2 = 68%, τ^2 = 1.1830, p = 0.01).

Neurophysiological Evaluations Outcome: MEP

Analysis from four clinical studies involving 49 participants demonstrated that 37% of patients exhibited improvements in MEP following BMMSC intervention (proportion: 0.37; 95% CI: 0.25–0.51), as illustrated in the forest plot (Figure 5). The random-effects model was employed to accommodate inter-study variability, but no statistical heterogeneity was detected (I^2 = 0%, τ^2 = 0, p = 0.57), indicating consistent results across studies.

Neurophysiological Evaluations Outcome: IVMC

Analysis from four clinical studies comprising a total of 53 participants revealed that 47% of patients demonstrated recovery of IVMC following BMMSC treatment (proportion: 0.47; 95% CI: 0.34–0.60), as depicted in the forest plot (Figure 6). The analysis was conducted using a random-effects model, which showed no heterogeneity among the studies (I^2 = 0%, τ^2 = 0, p = 0.54).

Neurophysiological Evaluations Outcome: AMR

Analysis from three clinical trials involving 33 patients demonstrated that 74% of participants showed signs of AMR following BMMSC therapy (proportion: 0.74; 95% CI: 0.39–0.92), as illustrated in the forest plot (Figure 7). The analysis applied a random-effects model to address inter-study variability, revealing a high heterogeneity index (I^2 = 73%, τ^2 = 1.0869, p = 0.02).

Urodynamics Evaluations Outcome: MCC

Analysis from three clinical trials comprising 33 participants demonstrated that 48% of patients showed improvement in MCC following BMMSC therapy (proportion: 0.48; 95% CI: 0.30–0.67), as depicted in the forest plot (Figure 8). The synthesis was conducted using a random-effects model to account for inter-study variability, which yielded relatively small heterogeneity index (I^2 = 41%, τ^2 = 0.0927, p = 0.19).

Urodynamics Evaluations Outcome: Bladder Compliance

Analysis from three clinical studies involving 33 participants revealed that 73% of patients experienced improvement in bladder compliance following BMMSC administration (proportion: 0.73; 95% CI: 0.55–0.85), as demonstrated in the forest plot (Figure 9). A random-effects model was employed to accommodate inter-study variation, resulting in low heterogeneity (I^2 = 24%, τ^2 = 0, p = 0.27).

Urodynamics Evaluations Outcome: Detrusor Pressure

Analysis from three clinical studies encompassing a total of 33 patients

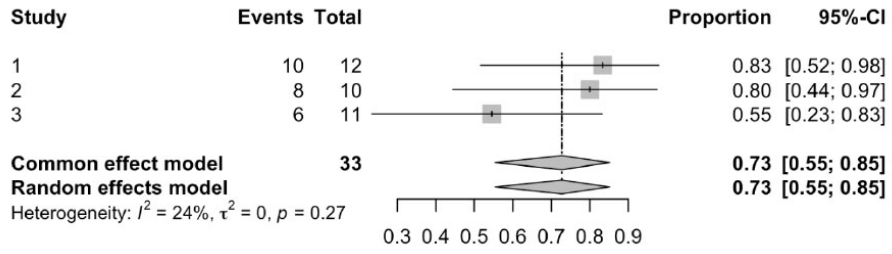

Figure 9. Forest plot of bladder compliance outcome.

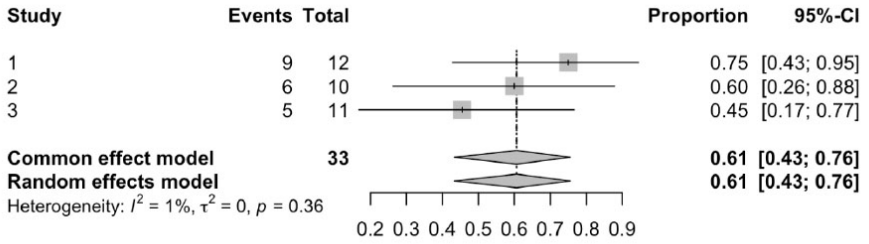

Figure 10. Forest plot of detrusor pressure outcome.

demonstrated that 61% of individuals exhibited improvement in detrusor pressure following BMMSC transplantation (proportion: 0.61; 95% CI: 0.43–0.76), as illustrated in the forest plot (Figure 10). The meta-analysis employed a random-effects model to account for between-study heterogeneity, yielding a negligible heterogeneity index (I^2 = 1%, τ^2 = 0, p = 0.36).

DISCUSSION

This meta-analysis presents convincing early evidence that autologous BMMSC treatment improves neurological and functional outcomes in individuals with chronic SCI. The most notable discovery is the 37% change in AIS grade among 123 patients, showing clinically significant neurological healing. This percentage is consistent with previous clinical results in which BMMSCs exhibited neurotrophic, anti-inflammatory, and axon-supportive functions.[10,16] Comparable improvements have also been reported in some studies of stem cell interventions for SCI that highlighting BMMSCs as one of the most promising cell types for functional recovery. Notably, this level of improvement occurs in a chronic patients that had previously been thought resistive to further recovery, highlighting the potential of regenerative methods beyond the subacute window.[1,9,17,18]

AIS is a reliable predictor of neurological recovery in SCI, with a shift in AIS grade indicating both structural and functional restoration of spinal cord pathways. BMMSC transplantation promotes this improvement through a variety of mechanisms, including neurotrophic factor secretion, immunomodulation, axonal guidance, and synaptic plasticity, even in chronically injured tissue with established glial scarring and inflammation.[15,16,19,20]

The paracrine activity of BMMSCs plays a pivotal role in enhancing this neural regeneration. BMMSCs release a wide range of growth factors, including BDNF, GDNF, NGF, VEGF, and IGF-1, which help in axon survival and sprouting, remyelination, and angiogenesis.[21–24] These factors improve the microenvironment around the lesion site, converting it from an inhibitory environment to one that promotes axonal regrowth and remyelination, both of which are necessary for restoring long-range connection and function.[23–26]

Furthermore, BMMSCs prevent subsequent damage by regulating the local immune response. Chronic SCI is characterized by prolonged inflammation and astroglial scarring, which limit axonal regrowth. BMMSCs have been demonstrated to downregulate pro-inflammatory cytokines (e.g., TNF-α, IL-1β) and upregulate anti-inflammatory mediators (e.g., IL-10), thereby reducing continuing neurodegeneration and stabilizing the lesion core.[27–29] Moreover, some studies also mentioned that BMMSCs had been able to promote intrinsic spinal cord plasticity by axonal sprouting and synapse formation.[12,13,20] BMMSC encourages the reconfiguration of spared pathways and may aid in the creation of alternative neuronal networks that can avoid the damaged zone. These rearranged circuits are most likely responsible for the increased motor and sensory scores, which translate into higher AIS grades.[6,10,15]

Neurophysiological outcomes further enhance these clinical observation results. Considerable recovery seen in SSEP, MEP, IVMC, and AMR indicates a multi-axonal healing process. The strong AMR response (pooled proportion: 0.74) found across investigations is very encouraging, indicating the re-establishment of peripheral motor circuits. This complements preclinical data that BMMSCs can influence both central and peripheral pathways.[2,12]

The improvements in SSEP and MEP corroborate the electrophysiological recovery of ascending and descending pathways, with modest variability. Vaquero et al. (2017, 2018)[6,10] showed some cases of subarachnoid BMMSC administrations resulted in normalization of SSEP latencies and amplitudes, with MRI evidence of structural remodeling. These findings support the idea that BMMSCs help with functional reconnection by bridging the lesion gap, regulating glial scarring, and creating a permissive environment.[13,16] The IVMC increase seen across patients indicates partial reactivation of corticospinal inputs, indicating that supraspinal integration is possible even in AIS A/B cases under chronic settings.[6,10]

Urodynamic outcomes highlight a less commonly discussed but clinically significant dimension of functional recovery. Increased MCC and bladder compliance, as well as decreased detrusor pressure, indicate partial restoration of autonomic function. The process most likely includes reinnervation of sacral micturition circuits and/or regulation of neurogenic inflammation in the bladder detrusor complex.[6,10,30,31]

Table 1. Characteristics of the 7 included studies

Author, Year	Country	Study Design			Mean Age	Duration from SCI to intervention, years	Duration of follow up
		Design	Sample Size	Inclusion Criteria			
Dai et al., 2013[12]	China	Double arm Clinical Trial Phase I/II	20	AIS A	22 - 54 34.7 ± 8.9	18 - 74 m 51.9 ± 18.3 month	6 months
El-Kheir et al., 2014[13]	Egypt	Controlled Single-blind Clinical Trial	50	AIS A-B	NA	NA	18 months
Medonca et al., 2014[7]	Brazil	Phase I Clinical Trial	14	AIS A	23 - 61 35.7 ± 9.9	1.5 - 15 month	6 months
Oh et al., 2016[14]	Korea	Phase III Clinical Trial	16	AIS A-B	NA	NA	6 months
Vaquero et al., 2016[15]	Spain	Phase I/II Clinical Trial	12	AIS A	25 - 58	3.17 - 26.75	12 months
Vaquero et al., 2017[6]	Spain	Phase I/II Clinical Trial	10	AIS B-D	34 - 59 42.20 ± 9.30	2.43 - 34.59 14.21 ± 9.88	12 months
Vaquero et al., 2018[10]	Spain	Phase II Clinical Trial	11	AIS A-D	28 - 62 44.91 ± 10.17	13.65 ± 14.79	10 months

AIS, association impairment scale; NA, not available; SCI, spinal cord injury

Despite these hopeful findings, considerable diversity in technique among the included research makes direct comparison difficult. Variations in cell dose (from 1×10^6 to 230×10^6 cells), method of injection (intrathecal, intramedullary, subarachnoid), damage degree, and length of SCI contribute to observed variability. This highlights the critical need for standardized procedures to improve treatment effectiveness and repeatability across sites. Another limitation is the absence of randomized controlled trials (RCTs) in the chronic SCI context. Most studies used pre-post comparisons with no control groups, making it difficult to definitely ascribe functional benefits to BMMSC treatment alone.

While the absence of RCTs and the variability of procedures present obstacles, the constant improvement in neurological, neurophysiological, and urodynamic measures warrants further exploration of BMMSCs. Future research should focus on defining dose-response relationships, improving administration techniques, and including long-term imaging and functional endpoints to evaluate efficacy and response durability. The data presented here are a significant step toward the standardization and clinical translation of stem cell therapy in SCI care.

These findings underscore the imperative for policymakers to incorporate regenerative medicine into current spinal cord injury care protocols. Evidence of functional recovery extending beyond the conventional subacute period indicates that healthcare systems ought to allocate resources for cell-based therapies in rehabilitation and chronic care programs. Policies ought to promote multicenter clinical trials, establish stem cell registries, and develop reimbursement systems to ensure fair access to advanced medicines.

BMMSC therapy signifies a transformative advancement for patients and rehabilitation experts, illustrating that significant neurological and autonomic enhancements can be attained even years post-injury. The combination of stem cell therapy with organized rehabilitation may improve results by facilitating activity-dependent plasticity. This highlights the significance of sustained monitoring, interdisciplinary follow-up, and patient education in primary care and rehabilitation policy to optimize outcomes and avert secondary problems.

CONCLUSION

This meta-analysis study found that BMMSC therapy promised treatment to enhance neurological outcomes in chronic SCI patients, with a notable proportion experiencing improvements in AIS grade, neurophysiological function, and urodynamic parameters. Further research, particularly well-designed RCTs, should be conducted to confirm the efficacy and safety of BMMSC therapy and address the variability in administration methods and dosages observed in current studies.

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No funds were received.

ETHICAL CONSIDERATION

No ethical clearance needed.

Table 2. Intervention protocols of included studies

Author, year	Intervention Protocol
Dai et al., 2013[12]	Intraspinal administration of 25 µl cell suspension (8 x 10^5 cells/µl), slowly injected to a depth of 3 mm at multiple sites in the central dorsal area across the junction of injured and normal spinal cord.
El-Kheir et al., 2014[13]	Intrathecal administration until meets cumulative target cell dose of 2 × 10^6 cells/kg, repeated monthly until target achieved (median was four injections, range was one to eight injections).
Medonca et al., 2014[7]	Intramedullary administration of 5 × 10^6 cells/cm3 (per lesion volume), that performed over a period of 5 minutes.
Oh et al., 2016[14]	Intramedullary administration of 1.6 x 10^7 autologous MSCs in 1 mL normal saline at the injury site, followed by 3.2 x 10^7 MSCs into the subdural space before dural closure.
Vaquero et al., 2016[15]	3–7 intramedullary administration (average, 4 microinjections/patient), volume of medicament in each microinjection ranged from 50– 1500 µl (average, 360 µL/microinjection,) with amount of administered cells per microinjection ranged from 5 × 10^6 MSCs to 150 × 10^6 MSCs (average, approx 36 × 10^6 MSCs). All patients received addition of subarachnoid administration of 30 × 10^6 MSCs 3 months after surgery.
Vaquero et al., 2017[6]	4 subarachnoid administration of 30 x 10^6 MSCs, repeated at months 4,7, and 10 (total administration of 120 x 10^6 MSCs for each patient).
Vaquero et al., 2018[10]	3 subarachnoid administrations of 100 × 10^6 MSCs, expanded and supported in autologous plasma, at months 1, 4, 7 of the study (total administration of 300 x 10^6 MSCs for each patient).

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to the content of this article.

AUTHOR CONTRIBUTIONS

Dewa Putu Wisnu Wardhana conceptualized the study, supervised the research, and performed critical revisions. Cindy Thiovany Soetomo conducted literature screening and initial drafting. Agung Bagus Sista Satyarsa contributed to data extraction, synthesis, and figures preparation. Sri Maliawan and Tjokorda Gde Bagus Mahadewa reviewed methodological quality and contributed to the final manuscript refinement. All authors approved the final version for submission.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

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