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Neurological, functional, and quality of life outcomes following combined mesenchymal stem cell and Schwann cell therapy in spinal cord injury: a 9-year experience

Mohammadhosein Akhlaghpasand[1†], Roozbeh Tavanaei[1†], Maede Hosseinpoor[1,2], Maryam Golmohammadi[1], Ida Mohammadi[1], Amir Ghaffari Jolfayi[1], Melika Hosseinpour[1], Bardia Hajikarimloo[1], Kaveh Oraii Yazdani[1], Alireza Zali[1] and Saeed Oraee-Yazdani[1*]

Abstract

Background Spinal cord injury (SCI) often results in severe disabilities and significant socioeconomic burdens.

Objective This study aimed to evaluate the effects and safety of co-transplantation of autologous bone marrow-derived mesenchymal stem cells (MSCs) and Schwann cells (SCs) via the intrathecal route in patients with complete spinal cord injury (SCI). The analysis focused on the therapy's impact across various SCI subgroups (cervical vs. thoracolumbar, subacute vs. chronic) and the factors influencing its efficacy.

Methods This case series evaluated 106 patients with complete SCI treated with combined cell therapy between August 2013 and September 2022, with a one-year follow-up. Safety profiles were assessed, and neurological and functional outcomes were measured using the American Spinal Injury Association (ASIA) scores, Spinal Cord Independence Measure (SCIM-III), and the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) at 6- and 12-month intervals post-injection. Multiple regression analysis was conducted to evaluate factors associated with outcomes.

Results Significant improvements were observed in ASIA scores (motor, light touch, and pinprick), SCIM-III scores (total and subscales), and WHOQOL-BREF scores after 12 months. These improvements were consistent across subgroups, regardless of injury level or duration. Multiple regression analysis indicated that improvements in ASIA motor scores were associated with injury level, while improvements in SCIM-III total and mobility scores were associated with time since injury and patient age.

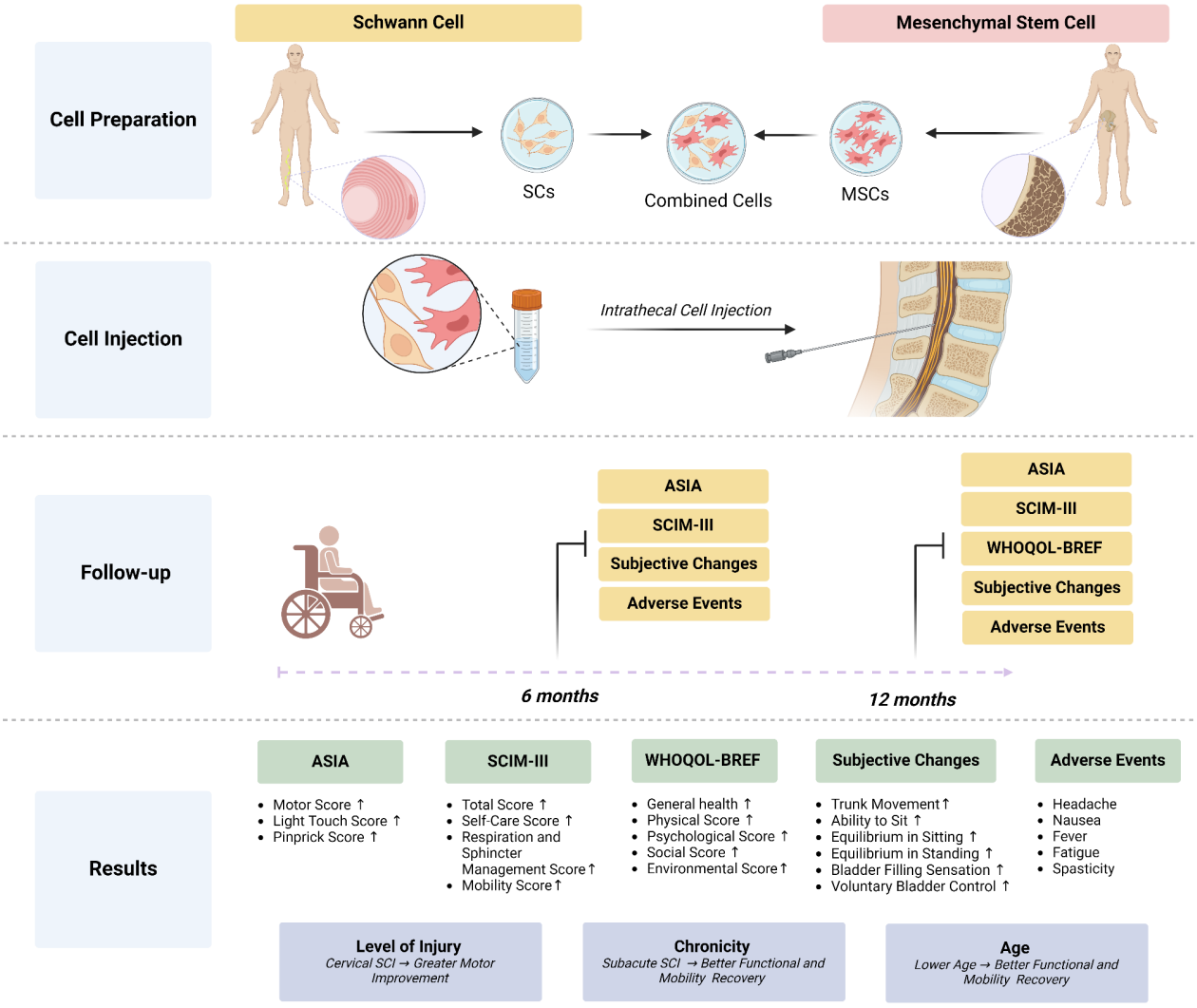
†Mohammadhosein Akhlaghpasand and Roozbeh Tavanaei contributed equally to this work and share the first authorship.

*Correspondence:
Saeed Oraee-Yazdani
Saeed_o_yazdani@sbmu.ac.ir

Full list of author information is available at the end of the article

Conclusions This study demonstrates significant neurological, functional, and quality of life improvements following combined cell therapy with autologous MSCs and SCs in patients with complete SCI. Future research should investigate potential synergies with other therapies and conduct comparative efficacy analyses.

Graphical abstract



Keywords Spinal cord injury, Stem cell therapy, Schwann cell, Mesenchymal stem cell

Introduction

Spinal cord injury (SCI) occurs in 13 cases per 100,000 population and causes partial or complete sensorimotor impairment [1, 2]. The SCI prognosis varies significantly depending on the extent of injury, which could be complete or incomplete. The former type of SCI is associated with poor clinical recovery, more severe functional loss, and higher costs compared with incomplete injury. Numerous pathophysiological factors hinder successful clinical and functional recovery in SCI, including neuronal and axonal death, scar tissue formation, and the presence of suppressive molecules [3, 4]. Therefore, given a lack of definite therapy, the development of novel treatment strategies for complete SCI to target different aspects of the multifaceted is an unmet need in the clinical arena [5].

Achieving successful clinical and functional recovery in SCI is closely tied to overcoming the barriers to axonal regeneration. These barriers are caused by several factors, including neuronal and axonal death, scar formation, and the presence of inhibitory molecules, among others. Addressing these challenges, therefore, requires a comprehensive and multifactorial approach. Over the years, numerous molecular strategies have been investigated,

yet they have faced challenges in demonstrating significant efficacy in clinical settings [3, 4, 6]. This disconnect between laboratory findings and clinical outcomes may stem from focusing on single pathophysiological mechanisms, despite the fact that SCI involves a complex interplay of multiple mechanisms and sequential pathological processes. To close this gap in clinical recovery, therapeutic interventions must target multiple aspects of SCI's complex pathology [3].

Various therapeutic approaches have been investigated to improve functional recovery after SCI, among which stem cell therapy has shown promising results. Previous studies have evaluated different cell types as potential effective therapeutic options in the treatment of SCI. Among them, mesenchymal stem cells (MSCs) have been widely investigated due mainly to their suitable characteristics for application in SCI treatment [7, 8]. These include the secretion of neuroprotective and immunomodulatory secretome, as well as low immunogenicity [9, 10]. In addition, some previous studies have supported the use of Schwann cells (SCs) in SCI and shown their neuroregenerative capacities. SCs, derived from the neural crest, are key candidates for use as supportive agents in conjunction with MSCs transplantation. They secrete various growth factors, including brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), nerve growth factor (NGF), and neurotrophin-3 (NT-3), all of which promote neural growth and regeneration. Additionally, SCs are essential in the formation of the myelin sheath in the peripheral nervous system (PNS), enhancing electrical signal transmission along axons and facilitating improved functional recovery [11]. Based on prior findings, the combined use of SC and MSC could increase the regenerative capacity and enhance the functional recovery after SCI compared with the use of each cell alone [12, 13].

Previously, we demonstrated the preliminary safety and efficacy of intrathecal co-administration of MSCs and SCs in patients with SCI [14, 15]. Therefore, the present study aimed to further elucidate the effects and safety profile of this therapeutic approach in a larger patient population.

Methods

Study design and participants

This study is a single-center observational case series approved by the Ethics in Medical Research Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.REC.1401.023). All patients with complete SCI undergoing combination intrathecal cell therapy using autologous bone marrow-derived MSCs and SCs in Shohada Tajrish hospital between Aug 20, 2013 and Sep 10, 2022, were followed for one year. Before performing any procedure, including the study intervention, cell culture, and biopsy specimen analysis, written informed consent was obtained from the participants. They were also given a thorough explanation about the study intervention, the experimental nature of the study, and potential associated adverse events (AEs).

The inclusion criteria were age between 18 and 65 years, cervical or thoracolumbar SCI, which could be chronic (more than 6 months after the injury) or subacute (14 days to 6 months after the injury), American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A, and availability of complete patient's hospital record. The exclusion criteria were coexisting underlying diseases, such as diabetes mellitus, neurological or psychiatric disorders, and cardiovascular diseases (e.g., angina pectoris, heart failure, or myocardial infarction), abnormal hepatic or renal function tests, penetrating spinal cord trauma or transection, the presence of active infection, such as pneumonia or urinary tract infection, positive test results for hepatitis C virus, human immunodeficiency virus, hepatitis B virus, cytomegalovirus, or sexually transmitted diseases, and prior (within the past ten years) or active malignancy.

Cell isolation, culture and characterization

The participants were hospitalized for SC and MSC harvest and were discharged one day after the procedure. The SC harvest was performed based on our modified protocol previously set up in our laboratory [15]. The protocol included the removal of sural nerve located in the calf region and was performed under general anesthesia. Under sterile conditions, the samples were placed in the Dulbecco modified Eagle's medium (DMEM, Gibco, Grand Island, NY, USA). They were then placed in a cold and sealed container and were transferred to the cell culture laboratory. The sural nerves were dissected and adjacent soft tissues were removed. The nerves were cut into pieces of 1–2 mm length and were exposed to dispase (2.4 U/mL; Sigma) and collagenase (1.4 U/mL; Sigma, St. Louis, MO, USA) at 37° C for 3 h. Thereafter, the cells were washed twice with DMEM/F12, mesh filtered, and incubated in fetal bovine serum (FBS)-free DMEM/F12 at 37° C and 5% CO_2 for five days. We gradually increased the FBS (Gibco) concentration in the culture medium up to 10% over one week after the fasting period.

The analysis of SC involved the utilization of S100 and glial fibrillary acidic protein (GFAP) immunocytochemical staining. After isolating the cells, they were fixed and permeabilized using 4% paraformaldehyde and 0.1% Triton X-100, respectively, sourced from Sigma-Aldrich. Following this, a blocking step ensued employing 10% goat serum (Gibco), followed by an overnight incubation at 4°C with either anti-S100 or anti-GFAP antibodies (both obtained from Santa Cruz Biotechnology, CA, USA). Subsequently, the samples underwent

incubation with an appropriate horseradish peroxidase-conjugated secondary antibody (Sigma-Aldrich) for 1 hour, followed by treatment with 3, 3'-diaminobenzidine (Sigma-Aldrich) to initiate the chromogenic reaction. Hematoxylin (Sigma-Aldrich) was utilized for nuclear counter-staining, and visualization of the cells was conducted through a light microscope.

For MSC harvest, each participant underwent the aspiration of 100–150 mL of bone marrow from the iliac crest. The Hanks Balanced Salt Solution (HBSS; Sigma) was used to dilute the samples (1:3). They subsequently underwent a density gradient (1:3 ratio) using Ficoll (1.077 g/L; Sigma). Thereafter, the samples were centrifuged at 400 x g for 40 min. After that, the mononuclear cell layer was separated and washed with HBSS. Following the removal of Ficoll, the cells were centrifuged three times for platelet removal and mononuclear cell isolation. To confirm the MSC isolation, the ability of cells to differentiate into adipogenic and osteogenic cells were evaluated. Moreover, flow cytometry was used to evaluate the cellular surface markers.

Cellular transplantation

Finally, the isolated MSCs (5×10^5 cells/mL) and SCs (5×10^5 cells/mL) were suspended in 6 mL of normal saline. Three weeks after harvest, patients referred to our institute for intrathecal cell administration. A lumbar puncture was performed at L4/L5 levels via a 24 G needle at the operating theatre. Following the needle insertion into the subarachnoid space (ascertained by observing the CSF), the cellular mixture (6 mL) was slowly injected through the lumbar puncture. The needle was kept in place for one minute to avoid the CSF leakage. One hour after the procedure, patients were discharged.

Outcome measures

Patients were evaluated in terms of safety and efficacy outcome measures at baseline, 6-month, and 12-month after the cell administration (quality of life was assessed only at baseline and 12 months after cell therapy). The efficacy outcome measures were ASIA (sensory and motor scales), Spinal Cord Independence Measure (SCIM-III; total score and self-care, mobility, and respiratory and sphincter management domain scores), subjective patient-reported improvements, and World Health Organization Quality of Life Brief Version (WHOQOL-BREF) questionnaire [15, 16]. The SCIM-III measure involves three subscales (19 items), including self-care, respiration and sphincter management (RSM), and mobility. The total SCIM-III score is the sum of all three subscales ranging from ranges from 0 (total dependence) to 100 (complete independence) [16]. The WHOQOL-BREF as a self-reported questionnaire that encompasses 26 questions, including two questions (Q1 and Q2) about general quality of life (QoL) and health as well as physical health, psychological health, social relationships, and environment domains. The questions are scored based on a five-point Likert scale. Linear transformation is then performed for domain scores (0-100 scale) [17]. All AEs were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4 in the present study.

Statistical analysis

Quantitative data were presented as mean ± standard deviation (SD), and qualitative data were expressed as frequency with percentage. Repeated measures analysis of continuous variables was performed using Friedman's test. The Wilcoxon signed-rank test was used to compare the WHOQOL-BREF domain scores between the baseline and 12-month after the injection. Subjective patient-reported outcomes were presented as dichotomous variables (whether improved or not according to the patient) and were compared between the baseline and 12-month after the injection using the McNemar's test. As the univariate analysis, the Mann-Whitney U test was utilized to compare changes in continuous variables over time (12 months– baseline) between various subgroups (cervical vs. thoracolumbar or subacute vs. chronic). For multivariate analysis, multiple linear regression was also performed on outcome measures that were significantly different between subgroups to assess the potential effect of baseline variables on their changes. The dependent variable was change (12 months– baseline) in efficacy outcome measures and the independent variables were age, sex, time elapsed since the injury (months), and the level of injury (cervical of thoracolumbar). The significance level was set at p-value < 0.05. STATA 15 (StataCorp.) was used to perform statistical analyses.

Results

Patients' characteristics

A total of 189 patients were screened for eligibility. A total of 83 patients did not meet the study criteria. Therefore, a total of 106 patients were recruited to this study between August 2013 and September 2022. The mean age of participants was 31.5 ± 10.0 years and the majority of them were male (n = 89, 84.0%). In terms of the level of injury, 32 (39.2%) and 74 (69.8%) patients had cervical and thoracolumbar SCI, respectively. A total of 77 patients had chronic SCI (72.6%) and 29 (27.4%) had subacute SCI. The baseline demographic and clinical characteristics of patients have been presented in Table 1.

Adverse events

Over the study period, 48 AEs were reported. These included headache (n = 34, 70.8%), nausea (n = 27, 56.3%), fever (n = 19, 39.6%), fatigue (n = 8, 16.7%), and spasticity (n = 5, 10.4%). All AEs were grade I or II in severity,

Table 1 Baseline demographic and clinical characteristics of the study cohort

Characteristic		Total ($n=106$)	Cervical ($n=32$)	Thoracolumbar ($n=74$)	Subacute ($n=29$)	Chronic ($n=77$)
Age years– mean (SD)		31.5 (10.0)	31.8 (11.9)	31.4 (9.2)	32.0 (9.8)	31.4 (10.2)
Sex– no. (%)	Male	89 (84.0%)	26 (24.5%)	63 (59.4%)	24 (22.6%)	65 (61.3%)
	Female	17 (16.0%)	6 (5.7%)	11 (10.4%)	5 (4.7%)	12 (11.3%)
Level of injury– no. (%)	Cervical	32 (30.2%)	-	-	6 (5.7%)	26 (24.5%)
	Thoracolumbar	74 (69.8%)	-	-	23 (21.7%)	51 (48.1%)
Duration of injury		23.9 (32.1)	33.0 (50.2)	20.0 (19.0)	3.9 (1.7)	31.4 (34.8)
Chronicity– no. (%)	Subacute (< 6 months)	29 (27.4%)	6 (5.7%)	23 (21.7%)	-	-
	Chronic (> 6 months)	77 (72.6%)	26 (24.5%)	51 (48.1%)	-	-
Cause of injury– no. (%)	Road traffic accident	77 (72.6%)	22 (20.8%)	55 (51.9%)	25 (23.6%)	52 (49.1%)
	Fall	21 (19.8%)	6 (5.7%)	15 (14.2%)	1 (0.9%)	20 (18.9%)
	Other traumatic	5 (4.7%)	3 (2.8%)	2 (1.9%)	3 (2.8%)	2 (1.9%)
	Non-traumatic	3 (2.8%)	1 (0.9%)	2 (1.9%)	0 (0.0%)	3 (2.8%)

SD: standard deviation; no.: number

Table 2 All adverse events observed throughout the study period with gradings based on common terminology criteria for adverse events version 4

Adverse event	Overall– no. (%)	Causal link with study intervention			Grade I	Grade II	Grade III
		Not related	Unlikely	Probable			
Headache	34 (70.8%)	34 (70.8%)	-	-	28 (58.3%)	6 (12.5%)	-
Nausea	27 (56.3%)	27 (56.3%)	-	-	27 (56.3%)	-	-
Fever	19 (39.6%)	16 (33.3%)	3 (6.3%)	-	12 (25.0%)	7 (14.6%)	-
Fatigue	8 (16.7%)	8 (16.7%)	-	-	7 (14.6%)	1 (2.1%)	-
Spasticity	5 (10.4%)	5 (10.4%)	-	-	5 (10.4%)	-	-

and all patients underwent outpatient treatment without any need for hospitalization. Additionally, no patient died over the follow-up period (Table 2).

Neurological improvement

Significant improvements in ASIA motor, light touch, and pinprick, scores were found over the study period. Across all participants, a statistically significant increase was observed in ASIA motor scores from a baseline mean of 40.7 (± 17) to 43.3 (± 15.9) at 12 months ($p<0.001$). Similarly, the light touch score improved from 57.6 (± 22.8) at baseline to 62 (± 24.7) at 12 months ($p<0.001$), while the pinprick score increased from 61 (± 23.3) to 66 (± 23.4) over the same period ($p<0.001$). (Fig. 1A–C; Additional File, Table S1)

Subgroup analysis also revealed significant improvement in ASIA motor ($p<0.001$), light touch ($p=0.002$), and pinprick ($p=0.013$) scores in the cervical subgroup across the study time points. The motor score increased from 23.9 (± 15.8) at baseline to 29.3 (± 16.1) at 12 months. Similarly, in the thoracolumbar subgroup, ASIA motor ($p<0.001$), light touch ($p<0.001$), and pinprick ($p<0.001$) scores showed significant improvement, with the motor score increasing from 47.9 (± 11.7) at baseline to 49.3 (± 11.5) at 12 months (Fig. 1A–C; Additional File, Table S1). Regarding the between-groups differences, the changes in ASIA motor score (12 months– baseline) were significantly different between the cervical (Δ: 5.4 ± 10.2) and thoracolumbar subgroups (Δ: 1.4 ± 3.7, $p=0.002$). No such difference was found for ASIA light touch ($p=0.699$) and pinprick ($p=0.897$) scores.

Concerning the chronicity, subgroup analysis showed a significant improvement in ASIA motor ($p=0.002$), light touch ($p<0.001$), and pinprick ($p<0.001$) scores in patients with subacute SCI over the study period. Similarly, there was a significant improvement in ASIA motor ($p<0.001$), light touch ($p<0.001$), and pinprick ($p<0.001$) scores over the study period in patients with chronic SCI. However, comparisons between subacute and chronic SCI patients revealed no significant differences in the degree of improvement from baseline to 12 months. Specifically, no significant differences were observed in the change in ASIA motor ($p=0.819$), light touch ($p=0.616$), or pinprick ($p=0.644$) scores between the two groups (Fig. 1A-C; Additional file 1: Table S2).

These results suggest that significant neurological recovery occurs over 12 months, regardless of injury chronicity. Notably, patients with cervical SCI exhibited greater motor function recovery compared to those with thoracolumbar SCI, while improvements in sensory function (light touch and pinprick) did not differ significantly across subgroups.

Functional improvement

Significant improvements were observed in SCIM III total scores and its subdomains, including self-care,

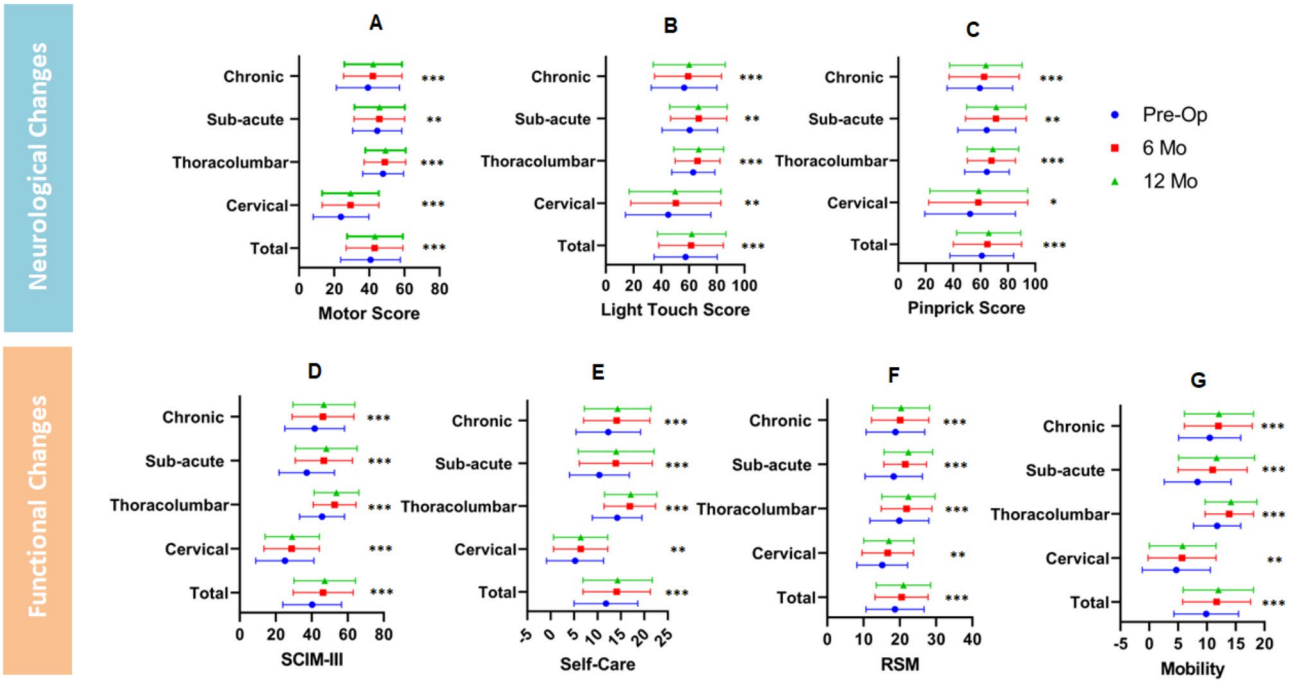


Fig. 1 Neurological (ASIA) and functional (SCIM-III) outcomes over the study period for the overall population and specific subgroups

RSM, and mobility, indicating enhanced functional independence in individuals with SCI over the study period. During the study, SCIM III total score increased significantly from 40.3 (± 16.3) at baseline to 47.2 (± 17.1) at 12 months ($p < 0.001$). Self-care scores improved from 11.8 (± 6.8) to 14.3 (± 7.4) ($p < 0.001$), RSM scores increased from 18.7 (± 8.0) to 21.0 (± 7.5) ($p < 0.001$), and mobility scores rose from 9.9 (± 5.6) to 12.0 (± 6.1) ($p < 0.001$), demonstrating significant changes in SCIMIII subdomains. (Fig. 1D-G; Additional File, Table S1)

Subgroup analysis based on the level of injury revealed significant improvements in the total SCIM III score and its subdomains in both cervical and thoracolumbar subgroups over the study period. In the cervical injury group, self-care ($p = 0.002$), RSM ($p = 0.006$), and mobility ($p = 0.002$) scores improved significantly, with the total SCIM III score increasing from 25.1 (± 16.2) at baseline to 29.1 (± 15.1) at 12 months. Similarly, the thoracolumbar subgroup showed significant gains in self-care ($p < 0.001$), RSM ($p < 0.001$), and mobility ($p < 0.001$), with the total SCIM III score rising from 45.8 (± 12.5) to 53.8 (± 12.4) at 12 months. However, no significant differences were observed between the cervical and thoracolumbar groups in changes from baseline to 12 months in total SCIM III score ($p = 0.136$) or in self-care ($p = 0.772$), RSM ($p = 0.772$), and mobility ($p = 0.065$) scores (Fig. 1D–G; Additional File, Table S1).

When considering chronicity, significant improvements in SCIM III total and all subdomain scores were observed in both subacute and chronic SCI groups. In the subacute SCI group, the SCIM III total score increased from 37.2 (± 15.4) at baseline to 48.1 (± 17.2) at 12 months ($p < 0.001$). Improvements were also observed in self-care ($p < 0.001$), RSM ($p < 0.001$), and mobility ($p < 0.001$) scores. Similarly, the chronic SCI group exhibited significant improvements, with the SCIM III total score increasing from 41.6 (± 16.6) to 46.8 (± 17.1) ($p < 0.001$). All subdomains, including self-care ($p < 0.001$), RSM ($p < 0.001$), and mobility ($p < 0.001$), showed significant improvement. There was a significant difference in changes (12 months– baseline) in total SCIM III score (Δ subacute: 10.9 ± 12.1; Δ chronic: 5.1 ± 9.3; $p = 0.009$) and mobility domain score (Δ subacute: 3.2 ± 3.5; Δ chronic: 1.6 ± 2.4; $p = 0.029$) between the subacute and chronic subgroups. No such a significant difference was found for self-care ($p = 0.055$), and RSM ($p = 0.055$) domains. (Fig. 1D-G; Additional file 1: Table S2)

These findings underscore that individuals with SCI experience functional recovery over the course of 12 months. While both the cervical and thoracolumbar subgroups demonstrated improvement, no significant differences were observed between the changes in these subgroups. Furthermore, although both subacute and chronic SCI patients showed improvements, subacute SCI patients exhibited greater gains in the total SCIM III and mobility scores over time.

Quality of life

Over the study period, significant improvements were observed across the general health, physical, social,

psychological, and environmental domains of the WHO-QOL-BREF. However, overall quality of life perception did not show a statistically significant increase. Specifically, quality of life perception rose from 37.8 (± 21.7) at baseline to 43.9 (± 16.6) at 12 months, though this change was not statistically significant ($p = 0.059$). In contrast, general health demonstrated a marked improvement, increasing from 23.8 (± 23.0) to 51.8 (± 31.8) over the same period ($p < 0.001$). Additionally, all QoL subdomains—physical, social, psychological, and environmental well-being—showed significant enhancements, each with p-values < 0.001.

Cervical subgroup showed significant improvements in Q2 ($p = 0.007$), physical ($p = 0.003$), psychological ($p = 0.008$), social ($p = 0.018$), and environmental ($p = 0.003$) domains at the 12-month follow-up compared with the baseline. Patients with thoracolumbar SCI also demonstrated significant improvements in Q2 ($p < 0.001$), physical ($p < 0.001$), psychological ($p < 0.001$), social ($p = 0.001$), and environmental ($p < 0.001$) domains at the 12-month follow-up compared with the baseline. No significant difference was found ($p > 0.05$) between the cervical and thoracolumbar groups in changes (12 months– baseline) in different domain scores. (Fig. 2A-F; Additional file 1: Table S3, S4)

In terms of chronicity, significant improvements in Q2 ($p = 0.004$), physical ($p = 0.005$), psychological ($p = 0.003$), social ($p = 0.003$), and environmental ($p = 0.003$) domains was observed in patients with subacute SCI at the 12-month follow-up compared with the baseline. There was also significant improvements in Q2 ($p = 0.001$), physical ($p < 0.001$), psychological ($p = 0.001$), social ($p = 0.010$), and environmental ($p < 0.001$) domains in the chronic subgroup at the 12-month follow-up compared with the baseline. There was no significant difference in changes (12 months– baseline) in WHOQOL-BREF domain scores between the subacute and chronic subgroups. (Fig. 2A-F; Additional file 1: Table S3, S4)

Despite no significant changes in overall quality of life perception, general health, physical, social, psychological,

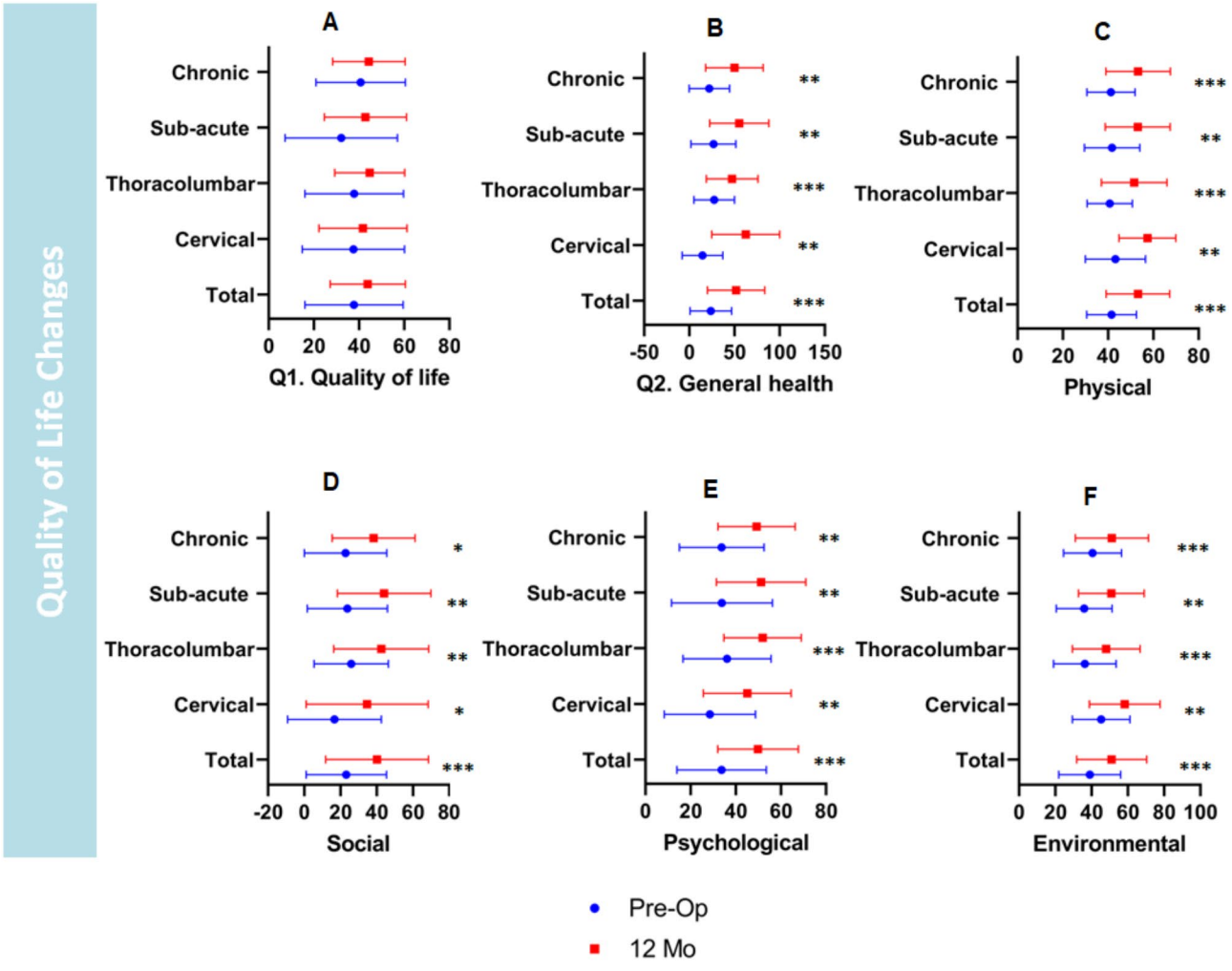


Fig. 2 Alterations in patients' quality of life (WHOQOL-BREF) throughout the study period, in the overall population and within specific subgroups

Table 3 Subjective patient-reported improvements over the study period

		Baseline	6-month	12-month	*P*-value[a]
Trunk Movement	No	37 (35.3%)	23 (22.4%)	23 (22.4%)	**0.003***
	Yes	68 (64.7%)	82 (77.6%)	82 (77.6%)	
Ability to Sit	No	31 (29.4%)	13 (12.9%)	13 (12.9%)	**< 0.001***
	Yes	74 (70.6%)	92 (87.1%)	92 (87.1%)	
Equilibrium in Sitting Position	No	87 (82.4%)	31 (29.4%)	31 (29.4%)	**< 0.001***
	Yes	18 (17.6%)	74 (70.6%)	74 (70.6%)	
Equilibrium in Standing Position	No	91 (86.7%)	51 (48.2%)	51 (48.2%)	**< 0.001***
	Yes	14 (13.3%)	54 (51.8%)	54 (51.8%)	
Bladder Filling Sensation	No	79 (75.0%)	58 (55.6%)	58 (55.6%)	**0.016***
	Yes	26 (25.0%)	47 (44.4%)	47 (44.4%)	
Voluntary Bladder Control	No	97 (91.7%)	76 (72.2%)	76 (72.2%)	**0.016***
	Yes	8 (8.3%)	29 (27.8%)	29 (27.8%)	
Any Anal Sensation	No	85 (80.6%)	73 (69.4%)	73 (69.4%)	0.125
	Yes	20 (19.4%)	32 (30.6%)	32 (30.6%)	
Voluntary Anal Contraction	No	94 (88.9%)	91 (86.1%)	91 (86.1%)	1.00
	Yes	11 (11.1%)	14 (13.9%)	14 (13.9%)	

[a] McNemar's test was performed to compare categorical outcomes at the 12-month follow-up with baseline

* Indicates statistically significant

and environmental domains showed significant improvements across all subgroups.

Multiple linear regression

Multiple linear regression analysis was also performed to evaluate the effect of different potential variables on changes in outcome measures. Changes in ASIA motor score at the 12-month follow-up was significantly associated with the level of injury (B= -4.487, $p = 0.002$). The changes in total SCIM-III score after 12 months was significantly associated with age (B = 0.326, $p = 0.005$) and time elapsed since injury (B= -0.111, $p = 0.016$). The changes in SCIM-III mobility subscale score after 12 months was also significantly associated with age (B = 0.081, $p = 0.008$) and time elapsed since the injury (B= -0.31, $p = 0.010$).

Subjective changes

A significant increase was found in the number of patients reporting a subjective improvement in trunk movement ($p = 0.003$), ability to sit ($p < 0.001$), equilibrium in sitting position ($p < 0.001$), and equilibrium in standing position ($p < 0.001$) at the 12-month follow-up compared with the baseline. Additionally, the number of patients who reported an acquired sense of bladder filling ($p = 0.016$) as well as the ability to voluntarily control the bladder ($p = 0.016$) was increased significantly at the 12-month follow-up compared with the baseline. No significant change in the number of patients who reported improvements in rectal filling sensation ($p = 0.125$) or voluntary anal contraction ($p = 1.00$) was found at the 12-month follow-up compared with the baseline. Changes in the subjective outcome measures are provided in Table 3.

Discussion

The present findings indicated significant improvements in neurological, functional, and QoL outcome measures in SCI patients after combined stem cell therapy. Moreover, many subjective patient-reported improvements were noted 12 months after the injection, including trunk movement, bladder contraction and sensation, and equilibrium (in sitting and standing). Additionally, all subgroups, including chronic, subacute, cervical, and thoracic complete SCI, showed significant improvements in ASIA, SCIM-III, and WHOQOL-BREF scores. Among subgroups, cervical SCI patients demonstrated a significantly greater improvement in ASIA motor score compared with the thoracolumbar subgroup. Moreover, subacute SCI patients showed better functional recovery in total SCIM-III and mobility scores compared with the chronic ones.

The major finding of this study was significantly improved ASIA motor, pinprick, and light touch scores after combined cell therapy. Many prior clinical studies have evaluated the effects of cell therapy on SCI. Abo El-kheir et al. [18] investigated the use of autologous bone marrow-derived cell therapy in patients with chronic SCI. Similar to our study, they found a significant improvement in ASIA motor, pinprick, and light touch scores as well as the functional independence measure in 15 patients with complete SCI. Vaquero J. et al. [19] studied the efficacy of intrathecal autologous MSC administration in 9 chronic SCI patient. Consistent with our findings, at the 10-month follow-up, they observed improvements in ASIA motor, pinprick, and light touch scores, as well as improvement in the SCI functional rating scale of the International Association of Neurorestoratology with its sphincter subscale. Furthermore, a significant increase in the neurogenic bowel dysfunction score and a non-significant decrease in the modified Ashworth scale scores were observed following MSC injection.

Another remarkable finding of this study was significant improvements in patient's QoL and functional outcome measures. To our knowledge, no prior study has evaluated the changes in QoL after stem cell therapy in SCI patients specifically. Different aspects of the patient's activities of daily living are affected following the SCI due to various associated complications, such as sensorimotor dysfunction, neuropathic pain, spasticity, and neurogenic bowel or bladder dysfunction [20–23]. Concerning this, previous findings have also demonstrated a complex relationship between QoL and physical impairment in patients with SCI [21, 22]. Additionally, SCIM-III as

the most reliable and valid measure of functional status in SCI patients showed significant improvements in all its three domains after combined cell therapy [16, 24]. Therefore, although there is a paucity of prior evidence, it seems that combined stem cell therapy could lead to significant enhancements in patient's QoL in a multifaceted manner. This is highly supported by significant improvements in patients' sensorimotor and bladder function as well as different domains of functional independence in the present study. Thus, it seems that combined cell therapy using MSCs and SCs could be a viable treatment option for SCI. Nevertheless, further evidence is highly required to investigate the potential additive effects of combined use of this therapy with other treatment strategies.

MSCs exert their therapeutic effects on SCI through various mechanisms. These cells are capable of secreting a range of anti-inflammatory molecules, including interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and prostaglandin E2 (PGE2), which inhibit the activation of immune cells such as T-cells and macrophages. Additionally, MSCs reduce the production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) [25]. Furthermore, MSCs protect neurons and axons from secondary damage following SCI by promoting the secretion of neurotrophic factors, including BDNF and glial cell line-derived neurotrophic factor (GDNF), which enhance the survival and differentiation of neural stem cells [26]. MSCs also play a role in mitigating glial scar formation, which can impede axonal regeneration post-SCI, by promoting the secretion of matrix metalloproteinases (MMPs), enzymes that degrade components of the extracellular matrix [27].

SCs, a type of glial cell, are critical for nerve regeneration and repair. In the context of SCI, SCs migrate to the injury site, where they facilitate axonal regeneration by releasing a variety of neurotrophic factors and extracellular matrix molecules [28]. These neurotrophic factors include NGF, BDNF, NT-3, fibroblast growth factor (FGF), CNTF, and GDNF [11]. The secretion of these factors enhances neuronal survival, promotes axonal outgrowth, and facilitates synapse formation. Additionally, SCs secrete extracellular matrix molecules, such as laminin and fibronectin, which create a conducive environment for axonal growth [11]. SCs further contribute to the remyelination of damaged axons by migrating to the injury site, guiding axons to their targets, and promoting the remyelination process [29, 30].

Effective recovery from SCI relies on addressing the complex barriers to axonal regeneration, which include neuronal loss, inhibitory scarring, and molecular factors that impede repair. Beyond the initial trauma, secondary injury processes such as inflammation and oxidative stress further damage neural tissue, making regeneration even more challenging [3–5]. Given these complexities, a combinatorial strategy is more effective than a single-target approach. MSCs and SCs offer complementary therapeutic benefits—MSCs support a neuroprotective environment, while SCs enhance axonal regrowth and remyelination. This study explores the co-administration of these cells as a synergistic approach to overcoming multiple barriers to SCI recovery, with the goal of improving both neuroprotection and functional restoration.

Patients with cervical SCI showed a significantly greater improvement in ASIA motor score after 12 months compared with the thoracolumbar subgroup. Many prior studies have demonstrated a better response to treatment in cervical SCI compared with thoracic injury [31, 32]. From an anatomical viewpoint, the cervical spinal cord has a higher white/gray matter ratio compared with the thoracic spinal cord. Given the higher concentration of myelinated axons in the white matter, the aforementioned difference might explain this finding to some extent [33–35]. Furthermore, the use of SCs as part of our combined cell therapy protocol further supports this hypothesis as SCs could mainly improve remyelination in damaged myelinated axons that are mostly located in the white matter [36, 37]. Another potential reason behind this finding could be differences in blood supply to the cervical and thoracic spinal cord. Richer blood supply to the cervical spinal cord due mainly to its extensive vascularization in comparison with the thoracic regions might potentially provide more oxygen and nutrients to the injured tissue and enhance recovery while preventing ischemia [38, 39].

Furthermore, the subacute subgroup in this study demonstrated a greater improvement in functional status as assessed using SCIM-III compared with the chronic one. This could be due to differences in neuroplasticity and regenerative capacity as well as the extent of inflammation. In subacute SCI, there is a more intense inflammatory response with higher levels of pro-inflammatory cytokines [40]. By contrast, chronic SCI is characterized by a reduced inflammatory response and the presence of reactive astrocytes with fibrotic scar tissue formation in the lesion core limiting the regenerative capacity of local axons. Hence, the anti-inflammatory effects of MSCs could be more beneficial in the subacute phase compared with the chronic one. In subacute SCI, there is also a greater potential for neural regeneration due to the presence of intact axons and neural connections. Chronic SCI, however, is characterized by significant tissue damage, loss of axons and neural connections, and a decrease in neuroplasticity capacity [41, 42]. In addition, functional clinical improvements in SCI patients during subacute to chronic phase transition have been reported previously, which tended to older age and more severe

injuries similar to our findings [43]. Thus, future studies with control arms are highly required to differentiate between the effects of cell therapy or the course of SCI itself in the specific population of patients with subacute SCI.

Bladder dysfunction is a common and serious complication of SCI, often leading to secondary issues such as urinary tract infections, bladder stones, and renal damage. MSCs have demonstrated potential in addressing SCI-related bladder dysfunction, as evidenced by clinical trials. In a study conducted by Mendonça et al., [44] the effects of intralesional administration of bone marrow-derived MSCs (BMSCs) were assessed in 14 patients with chronic SCI. While an increase in bladder capacity was observed six months post-procedure, this change did not reach statistical significance. However, a significant improvement in bladder compliance relative to baseline measurements was reported. Similarly, Vaquero et al. [19] investigated the safety and efficacy of intrathecal administration of autologous BMSCs in 11 patients with chronic SCI. Ten months following the initial intrathecal injection, 66.6% of the patients exhibited a reduction in post-void residual volume and an improvement in bladder compliance during the filling phase.

Preclinical studies investigating the application of stem cell therapy for urinary dysfunction in SCI have elucidated several potential mechanisms. Hu et al. conducted intravenous injections of BMSCs in rats and observed the presence of labeled BMSCs in the dorsal gray commissure of the L3-4 spinal segments. They proposed that the recovery of voiding function was likely due to the development of new voiding reflex pathways resulting from the reorganization of synaptic connections [45]. Similarly, Erdogan et al. examined the effects of intralesional injections of fetal allogeneic umbilical cord MSCs in rats with incomplete SCI, reporting a reduction in inflammation, lamina muscularis thickness, and bladder wall fibrosis [46]. Additionally, Mitsui et al. demonstrated that improvements in bladder function following the administration of neuronal and glial restricted precursors were linked to alterations in lumbosacral circuitry. This was attributed to regional neuroprotection, which promoted sparing and sprouting of descending pathways [47]. However, due to the heterogeneity among existing studies, further research is needed to definitively elucidate the mechanisms underlying the effects of cell therapy on bladder function.

The administration of MSCs may lead to adverse effects such as fever, headache, nausea, vomiting, and pain, all of which can negatively impact the patient's quality of life. The molecular mechanisms responsible for these adverse effects involve a range of molecules and signaling pathways. Fever is a common side effect following MSC therapy in patients with SCI, and it is primarily associated with the release of proinflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) from the injected cells [48, 49]. These cytokines activate the hypothalamic-pituitary-adrenal (HPA) axis, stimulating the production of prostaglandins (PGs) via activation of the cyclooxygenase (COX) pathway. The resulting increase in PGs induces fever by promoting the production of cyclic adenosine monophosphate (cAMP) and raising the set-point temperature in the hypothalamus [50]. In addition, prostaglandins can directly activate nociceptors and stimulate the release of calcitonin gene-related peptide (CGRP) and substance P from sensory neurons, leading to vasodilation and increased cerebral blood flow. This vasodilation can trigger headaches by stretching blood vessels and activating pain receptors [51]. Fever may also be exacerbated by the activation of toll-like receptors (TLRs) on the surface of MSCs, which stimulates immune cells to release additional proinflammatory cytokines [49].

Intrathecal injection via lumbar puncture is a less invasive and clinically feasible method for cell delivery in cervical and thoracolumbar spinal cord injuries. It prevents further trauma to the injured cord while ensuring targeted cell accumulation at the lesion site. Studies have demonstrated that LP-transplanted cells primarily localize in the intrathecal space, distributing along the lumbar, thoracic, and cervical regions, promoting neuroprotection and functional recovery. MSCs delivered this way effectively reach contused spinal tissues, reducing cyst formation and injury size, demonstrating significant therapeutic benefits [52–54].

This study aimed to evaluate a large population of SCI patients to assess the patterns of change across different subgroups of complete SCI, including subacute, chronic, cervical, and thoracolumbar injuries. These patients were followed up over an extended period to investigate the effects of stem cell therapy on quality of life. This approach allowed for subgroup analysis to explore differences in treatment response among SCI patients undergoing combined cell therapy with MSCs and SCs.

Despite its strengths, this study had several limitations. It was based on an observational research without a control group, limiting the ability to compare outcomes across different treatment groups or interventions. Additionally, the possibility of a placebo effect—where patients, aware of receiving an experimental therapy, may report improved outcomes—cannot be ruled out. To mitigate these bias, objective measures such as the ASIA scores and SCIM-III were used. However, the evaluation of quality of life (WHOQOL-BREF) in this study may be influenced by these biases, where patients report improved well-being based on expectations rather than actual treatment efficacy. Moreover, factors like natural recovery, psychological adaptation, and external

influences could affect WHOQOL-BREF scores, making it challenging to attribute observed improvements solely to the intervention.

Moreover, as this study was conducted at a single center with a consistent research team, future multicenter studies are needed to validate these findings across diverse healthcare settings. Another limitation is the uncertainty surrounding the better treatment response observed in the subacute subgroup for certain outcome measures, which could be attributed to either the intervention or the natural course of SCI recovery. We recommend that future multicenter controlled trials include larger patient population and adopt rigorous, controlled evaluation methods to address these limitations.

Conclusions

Combined cell therapy using MSCs and SCs significantly improved neurological and functional outcome as well as the QoL in patients with complete SCI. All subgroups of SCI, including cervical, thoracolumbar, subacute, and thoracolumbar showed significant improvements after 12 months compared with the baseline. Moreover, differences in response to combined cell therapy were noted between different study subgroups that require further evidence from future multicenter randomized investigations with control arm.

Supplementary Information

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Supplementary Material 1: Additional file 1: Table S1-S4: Detailed changes in ASIA, SCIM-III, and WHOQOL-BREF outcome measures for the overall population and specific subgroups

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Author contributions

M.A: Conceptualization, Methodology, Investigation; RT: Conceptualization, Methodology, Writing-review and editing; M.H: Writing original draft, Investigation; M.G: Investigation; I.M: Investigation, Formal analysis; A.G: Data curation; M.H: Investigation; BH: Writing original draft; K.O-Y: Supervision; A.Z: Supervision; S.O-Y: Supervision, Funding acquisition, Project administration.

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Data availability

The data supporting the findings of this study are stored in the Functional Neurosurgery Research Center repository, and more detailed results of the analysis are provided in the supplementary material. The study's data are available from the corresponding author upon reasonable request.

Declarations

Research ethics and patient consent

This study was approved by the Ethics Committee for Medical Research at Shahid Beheshti University of Medical Sciences (Approval ID: IR.SBMU.REC.1401.023) on November 13, 2022, under the title "Comparison of the Efficacy of Autograft Bone Marrow Stem Cells and Schwann Cell Transplantation in Patients with Chronic and Subacute Spinal Cord Injuries."

Consent for publication

Before conducting any procedures—including the study intervention, cell culture, and biopsy specimen analysis—written informed consent was obtained from all participants. They were provided with a comprehensive explanation of the study intervention, its experimental nature, the potential associated adverse events (AEs), and were informed that permission had been granted for the publication of all data and images in a scientific article.

Conflict of interest

The Authors declare that there is no conflict of interest.

Author details

[1]Functional Neurosurgery Research Center, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, PO box: 1988873554, Tehran, Iran
[2]Stem Cell Technology Research Center (STRC), Iran University of Medical Sciences (IUMS), Tehran, Iran

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