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Research Article

Efficacy and Safety of Exosomes from Wharton's Jelly-Derived Mesenchymal Stem Cells in Patients with Spinal Cord Injury.

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Running title: Exosome Therapy in Spinal Cord Injury

Abstract

Backgroud: Traumatic spinal cord injury (SCI) is a pathological condition characterized by neurological impairments, the severity of which is contingent upon the level and extent of the injury. In addition to these impairments, SCI is frequently associated with autonomic dysfunctions and complications affecting the cardiovascular and gastrointestinal systems, leading to debilitating consequences such as urinary and bowel incontinence and spasticity, significantly diminishing patients' quality of life.

Aim: This study aimed to evaluate the safety and therapeutic efficacy of mesenchymal stem cell-derived exosomes (MSCdE) in patients with SCI.

Methods: Sixteen patients (mean age: 26.25 ± 4.89 years) with SCI resulting from combat-related injuries were enrolled. Of these, 2 patients (12.5%) had lumbar injuries, 11 (68.75%) had thoracic injuries, and 3 (18.75%) had cervical injuries. Exosome administration was performed in 6 treatment cycles over a 4.5-month period. Each cycle involved the intrathecal injection of 3 ml (30 billion) and intramuscular injection of 10 ml (30 billion) of exosomes. Patients were monitored for 1 year following the intervention. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Neurological function was evaluated using the American Spinal Injury Association Impairment Scale (ASIA), spasticity using the Modified Ashworth Scale (MAS), motor and cognitive function using the Functional Independence Measure (FIM), and urinary and bowel incontinence using the Wexner Incontinence Score and Qualiveen Short Form (SFQ). All assessments were conducted by a multidisciplinary team comprising a neurosurgeon and a specialist in physical therapy and rehabilitation.

Results: No serious adverse events were reported throughout the treatment and follow-up period. Minor side effects, such as low-grade fever and localized pain, were observed, classified as CTCAE v5.0 Grade 1, and resolved spontaneously within 24 hours without medical intervention. Statistically significant improvements were noted in all clinical parameters. FIM motor scores increased from 26.75 ± 9.81 pre-treatment to 43.88 ± 17.01 post-treatment ($p < 0.01$). ASIA motor scores improved significantly from 47.00 ± 21.15 to 56.00 ± 18.74 ($p < 0.001$), and ASIA sensory scores (light touch/pin-prick) increased from 66.06/66.25 to 77.56/79.75 ($p < 0.001$). MAS values (right/left) decreased from 7.00/6.94

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to 4.56/4.50 ($p < 0.001$), indicating reduced spasticity. A statistically significant improvement in urinary and bowel incontinence scores (SFQ/Wexner) was observed, improving from 31.38/19.75 to 27.56/16.44 ($p < 0.001$).
Conclusion: The results of this study demonstrate that MSCdE therapy is both safe and effective in the treatment of SCI. However, further large-scale randomized controlled trials are warranted to corroborate these findings and establish more robust clinical evidence.

Keywords : Spinal Cord Injury; Exosomes; Stem Cells; Cellular Therapy.

INTRODUCTION

Traumatic spinal cord injury (SCI) causes severe motor and sensory deficits along with systemic complications such as autonomic dysregulation and organ dysfunction, significantly reducing quality of life [1,2]. Globally, SCI affects 250,000 to 500,000 individuals annually, with higher incidence rates among adolescents and young adults, particularly from traumatic events like motor vehicle accidents and sports injuries [3-7]. SCI in young patients leads to long-term physical, psychological, and social challenges, with frequent secondary complications such as infections and pressure ulcers, complicating recovery [8,9].

SCI progresses through primary injury—mechanical trauma that damages axons, blood vessels, and cell bodies—and secondary injury, involving inflammation, oxidative stress, and excitotoxicity that worsen the damage and inhibit recovery [10-14]. Effective treatments must address both phases, particularly by targeting inflammation and oxidative damage [15].

Given the limited regenerative capacity of the spinal cord, regenerative medicine, especially mesenchymal stem cells (MSCs), has shown potential for SCI treatment due to their immunomodulatory and regenerative properties [16,17]. On the other hand, MSC-derived exosomes (MSCdE), small vesicles carrying bioactive molecules, offer a novel therapeutic approach by enhancing neuroprotection, reducing inflammation, and promoting regeneration [18-21]. Their immunomodulatory effects also mitigate detrimental immune responses [22].

This phase 1 study assesses the safety and preliminary efficacy of MSCdE in SCI patients, focusing on improvements in neurological function, spasticity, motor and cognitive abilities, and incontinence. These findings aim to guide future randomized controlled trials.

MATERIALS AND METHODS

Study Design

This Phase I study was a prospective, longitudinal clinical trial conducted at Romatem Physical Therapy and Rehabilitation Hospitals (Bursa & Kocaeli). The study was approved by the institutional review boards of the participating institutions (protocol number: 22122023.1). Written informed consent was obtained from the patients' legal representatives, in accordance with the Helsinki Declaration. Baseline demographic and clinical data, including age, gender, duration since spinal cord injury (SCI), and relevant medical history, were collected.

Patient Population

The study included 16 patients aged between 19 and 35 years (mean age: 26.25 ± 4.89) who sustained SCI as a result of combat injuries. The distribution of injury levels was cervical in 3 patients (18.75%), lumbar in 2 patients (12.5%), and thoracic in 11 patients (68.75%). All patients had previously undergone surgical decompression and, when necessary, spinal instrumentation within the acute or subacute phase following their injury. Despite participating in rehabilitation programs for 6 to 12 months, patients did not experience significant functional improvements. MSC-derived exosome (MSCdE) treatment was initiated 8 to 14 months after the SCI.

Enrollment Criteria

Inclusion criteria required that SCI be confirmed through imaging studies (e.g., computed tomography (CT) or magnetic resonance imaging (MRI)) and neurological examination. Exclusion criteria included the presence of focal central nervous system lesions (e.g., neoplastic lesions) or chronic systemic diseases that required ongoing pharmacotherapy. Prior to the initiation of MSCdE therapy, patients were thoroughly evaluated by specialists in neurosurgery and physical therapy and rehabilitation to ensure suitability for the treatment.

Procedure

The MSCdE therapy comprised intrathecal (i.t.) and intramuscular (i.m.) injections. The procedure was carried out only when patients were stable and free from contraindications for sedoanalgesia or severe infections. Intramuscular injections were performed under ultrasound guidance to accurately target affected muscle groups. Each patient underwent a total of 6 rounds of treatment, with each round involving the administration of 30 billion (3 ml) i.t. exosomes and 30 billion (10 ml) i.m. exosomes. The detailed treatment schedule is summarized in **Table 1**.

Table 1. Administration schedule

Rounds	Route	WJ-MSC
Round 1	IT	30 × 10^9 exosomes in 3 mL
	IM	30 × 10^9 exosomes in 10 mL
Round 2 (week 2)	IT	30 × 10^9 exosomes in 3 mL
	IM	30 × 10^9 exosomes in 10 mL
Round 3 (week 6)	IT	30 × 10^9 exosomes in 3 mL
	IM	30 × 10^9 exosomes in 10 mL
Round 4 (week 10)	IT	30 × 10^9 exosomes in 3 mL
	IM	30 × 10^9 exosomes in 10 mL
Round 5 (week 14)	IT	30 × 10^9 exosomes in 3 mL
	IM	30 × 10^9 exosomes in 10 mL
Round 6 (week 18)	IT	30 × 10^9 exosomes in 3 mL
	IM	30 × 10^9 exosomes in 10 mL

Exosome Protocols

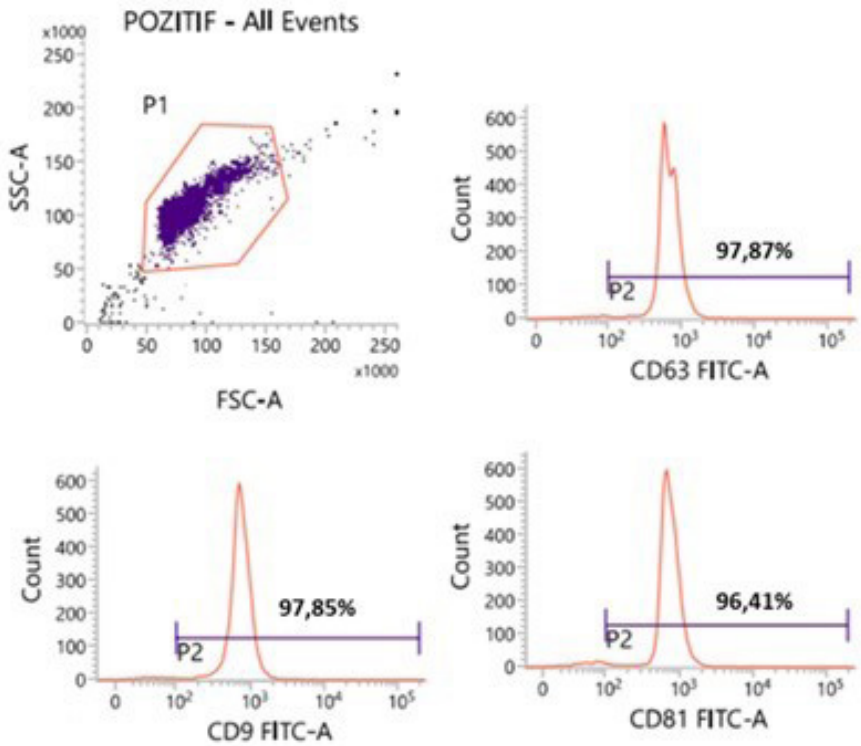
Isolation of Exosome Protocols

Mesenchymal stem cells are cultured in serum-free medium to prevent contamination from serum-derived proteins, and concentrated amounts of exosomes are obtained. Exosomes are produced under 5% CO_2 at 37 °C for 24–48 hours, after which the serum-free medium is collected. The medium is first centrifuged at 400 g for 10 minutes to remove residual cells, and the supernatant is retained for the next step. In the second step, the supernatant is centrifuged at 2000 g for 20 minutes and then passed through a 0.22 µm syringe filter. In the third step, the supernatant is centrifuged at 10,000 g for 70 minutes. Finally, the supernatant is ultracentrifuged at 110,000 g for 120 minutes, and the pellet containing the exosomes is collected. Each pellet is resuspended in 1 ml of Dulbecco's Phosphate Buffered Saline (dPBS) and vortexed. All pellets are then combined into a single tube and ultracentrifuged again at 110,000 g for 120 minutes. Depending on the pellet amount, exosomes are resuspended in 500–1000 µl dPBS and stored at –80 °C or –152 °C for up to one year.

Flow of Exosome Protocols

The analysis of exosomes by flow cytometry is performed according to the manufacturer's protocol of the Tetraspanin Exo-Flow Capture Kit. Briefly, exosomes are first captured using antibody-coated magnetic beads targeting tetraspanin markers. Following the capture step, the bead–exosome complexes are incubated with FITC-conjugated detection antibodies. After washing to remove unbound reagents, the samples are analyzed on a BD FACSCanto II flow cytometer to confirm the expression of surface markers such as CD9, CD63, and CD81. (BD FACSCanto II, USA). (**Figure 1**)

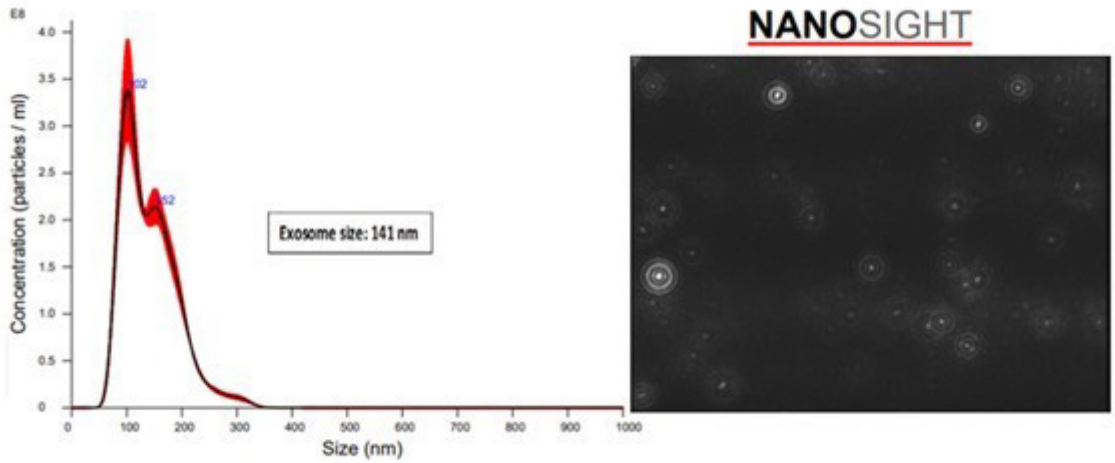
Figure 1. Flow Cytometry analysis of exosomes



NTA of Exosome Protocols

Exosomes typically range in size between 50 and 200 nm. Based on their diameter, they are categorized as small (50–100 nm), medium (100–150 nm), and large (150–200 nm). The size distribution and concentration of exosomes are determined using nanoparticle tracking analysis (NTA). Following isolation, exosomes are resuspended with the aid of a pipette. Depending on the concentration, the samples are diluted with dPBS and transferred into 2 ml cryovials, with a final volume adjusted to 1 ml. The prepared sample is then loaded into the device using a 1 ml syringe, and particle concentration as well as size distribution are measured. The instrument settings of the NTA device (NanoSight NS300, Malvern Panalytical, UK) are optimized and recorded. (**Figure 2**)

Figure 2. Nanoparticle Tracking Analysis of exosomes



Clinical Evaluation

Pre-treatment Assessment

A comprehensive pre-treatment evaluation was conducted by a multidisciplinary team, including neurosurgeons and physical and rehabilitation specialists. Neurological and functional status was assessed using the American Spinal Injury Association (ASIA) Impairment Scale, which categorizes impairment based on motor and sensory function. Spasticity was measured using the Modified Ashworth (MA) Scale, which quantifies muscle tone. The impact of gastrointestinal and urinary incontinence on the quality of life was evaluated using the Wexner Incontinence Score (WIS) and the Qualiveen Short Form (SFQ), respectively. Overall quality of life was assessed using the Functional Independence Measure (FIM), which evaluates self-care, mobility, and cognitive function.

Safety Evaluation

Safety measures were closely monitored throughout the treatment procedure and during the post-procedure follow-up period. Key indicators of safety included monitoring for infection signs such as fever, elevated C-reactive protein levels, and leukocytosis. Additionally, potential complications related to anesthesia and analgesia, wound infections, and allergic reactions or shock were assessed. Long-term safety was evaluated over a one-year period, focusing on the incidence of infections, cancer development, neuropathic pain, and signs of neurological degeneration. Adverse events were classified and documented according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).

Follow-up Assessment

Follow-up assessments were conducted to evaluate the efficacy of MSCdE therapy. Neurological and functional outcomes were assessed using the same scales as in the pre-treatment evaluation. Spasticity was measured with the MA Scale, and the effects of incontinence on quality of life were re-evaluated using the WIS and SFQ. Functional recovery and overall quality of life were assessed using the FIM. Additional follow-up included a thorough examination for neuropathic pain, urinary tract infections, secondary infections, and pressure ulcers to provide a comprehensive overview of the patients' progress and overall well-being.

Statistical Analysis

Statistical analyses were performed to evaluate changes in the FIM Scale, MA Grading, ASIA Score, WIS, and SFQ scores from pre-intervention to post-intervention. Repeated measures analysis of variance (ANOVA) was used to assess differences between pre-treatment and measurements taken at 1 week, 1 month, 2 months, 4 months, and 6 months post-intervention. Significant differences were further analyzed using the Bonferroni post-hoc test to determine specific group differences. All statistical analyses were conducted using SPSS software version [specific version], with a significance level set at $p < 0.05$.

RESULTS

Safety and Adverse Events

The administration of mesenchymal stem cell-derived exosomes (MSCdE) was well-tolerated by all participants in this Phase I study. The procedure did not result in any significant adverse effects, indicating a favorable safety profile for MSCdE treatment.

During the course of the study, six patients experienced minor, transient complications following the intramuscular administration of MSCdE. These complications included subfebrile fever (slightly elevated body temperature), moderate headache, and localized muscle soreness. All of these events were categorized as CTCAE v5.0 Grade 1, reflecting their low severity [26]. Subfebrile fever, a mild increase in body temperature, was the most common issue, often associated with the body's response to the introduction of therapeutic agents. Moderate headaches were reported as occasional and resolved spontaneously. Muscle soreness was localized to the injection sites and was consistent with typical responses to intramuscular injections.

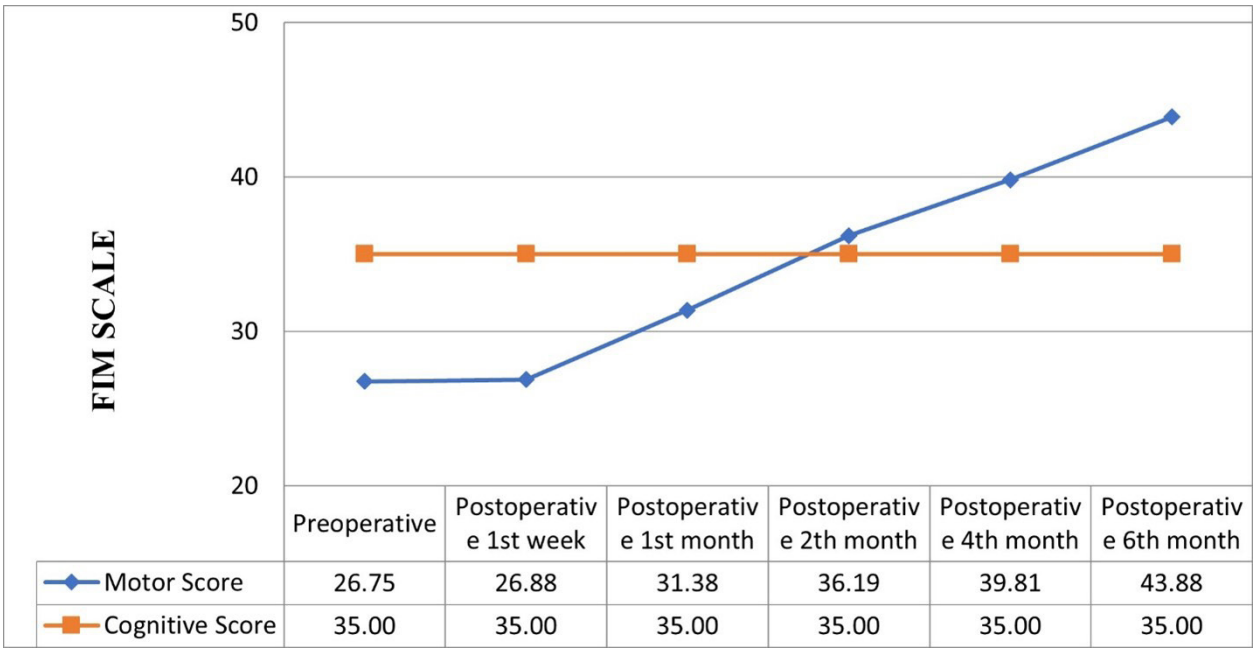
These minor complications were managed effectively with symptomatic treatment when necessary, and no additional medical interventions were required. Importantly, these events were short-lived, resolving within a few days without any long-term consequences or the need for further medical attention.

Throughout the one-year follow-up period, no further safety concerns or adverse events were reported. The absence of severe complications or persistent issues suggests that MSCdE administration is relatively safe and well-tolerated in the study population. The ongoing monitoring and evaluation of participants during this follow-up period confirmed that the treatment did not lead to any delayed adverse effects or long-term health problems.

FIM Scale Scores

Figure 3 presents a visual representation of the changes in the Functional Independence Measure (FIM) Motor and Cognitive Scores from pre-intervention to various post-intervention time points. A notable increase in FIM Motor Scores was observed after the first week of MSCdE administration. However, no significant changes were detected in FIM Cognitive Scores across the assessment periods.

Figure 3. Changes observed in the pre-test and post-test means of the patients' FIM Motor and Cognitive Scores.



	Preoperative	Postoperative 1st week	Postoperative 1st month	Postoperative 2th month	Postoperative 4th month	Postoperative 6th month
Motor Score	26.75	26.88	31.38	36.19	39.81	43.88
Cognitive Score	35.00	35.00	35.00	35.00	35.00	35.00

Table 2 summarizes the results of the repeated-measures analysis of variance (ANOVA) for FIM Motor Scores. The analysis revealed a statistically significant improvement in scores from pre-intervention to post-intervention assessments ($F=59.231$, $p<0.001$). Post-hoc Bonferroni testing showed that while no significant differences were found between pre-test and the 1-week post-test scores, significant increases were observed at subsequent time points. Specifically, significant improvements were seen from the 1-month to the 6-month assessments, indicating a progressive enhancement in motor function over time. The FIM Cognitive Scores remained consistent at 35 points across all time points, so no further analysis was necessary for this measure.

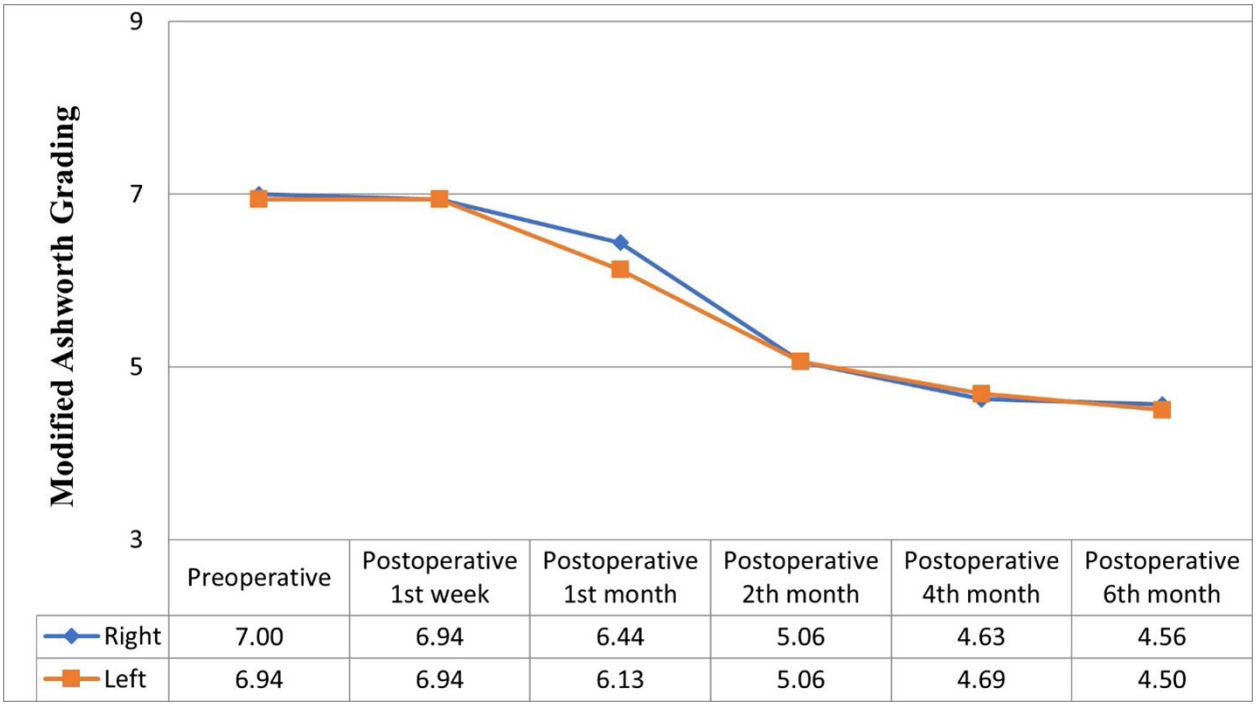
Table 2. Repeated measures ANOVA results for changes observed in patients' FIM Motor Score values before and after the intervention.

Time	Mean	SD	F	p	η^2_p	post-hoc
Pre-op (1)	26,75	9,81	59,231	< .001	0,798	1 < 3, 4, 5, 6 2 < 3, 4, 5, 6 3 < 4, 5, 6 4 < 5, 6 5 < 6
Post-op 1st week (2)	26,88	10,13				
Post-op 1st month (3)	31,38	12,50				
Post-op 2nd month (4)	36,19	14,60				
Post-op 4th month (5)	39,81	15,76				
Post-op 1st year (6)	43,88	17,01				

Modified Ashworth Scale (MA) Scores

Figure 4 depicts the changes in Modified Ashworth (MA) Scale scores for muscle spasticity, measured separately for right and left muscle groups. A consistent decrease in MA scores was observed starting from the first week after the intervention, with a reduction in the rate of decrease noted after the second month.

Figure 4. Changes observed in the pre-test and post-test means of the patients' Modified Ashworth Grading Right and Left values.



	Preoperative	Postoperative 1st week	Postoperative 1st month	Postoperative 2th month	Postoperative 4th month	Postoperative 6th month
Right	7.00	6.94	6.44	5.06	4.63	4.56
Left	6.94	6.94	6.13	5.06	4.69	4.50

Table 3 presents the repeated-measures ANOVA results for MA Scale Right scores. The analysis indicated a significant difference in scores before and after the intervention ($F=23.421$, $p<0.001$). Post-hoc Bonferroni testing identified significantly higher MA scores at pre-test, 1-week post-test, and 1-month post-test compared to scores obtained at 2 months, 4 months, and 6 months. This suggests an initial decrease in spasticity that stabilized over time.

Table 3. Repeated measures ANOVA results for the changes observed in the Modified Ashworth Grading Right values of the patients before and after the intervention.

Time	Mean	SD	F	p	η^2_p	post-hoc
Pre-op (1)	7.000	4.899	23.421	< .001	0.61	1 < 4, 5, 6 2 < 4, 5, 6 3 < 4, 5, 6
Post-op 1st week (2)	6.938	4.919				
Post-op 1st month (3)	6.438	4.472				
Post-op 2nd month (4)	5.063	3.678				
Post-op 4th month (5)	4.625	3.500				
Post-op 1st year (6)	4.563	3.521				

Table 4 provides similar results for MA Scale Left scores, with a statistically significant difference observed (F=19.698, p<0.001). Post-hoc testing confirmed that MA scores at pre-test, 1-week post-test, and 1-month post-test were significantly higher than scores obtained at later time points, indicating a significant reduction in spasticity following MSCdE treatment.

Table 4. Repeated measures ANOVA results for the changes observed in the Modified Ashworth Grading Left values of the patients before and after the intervention.

Time	Mean	SD	F	p	η^2_p	post-hoc
Pre-op (1)	6.94	4.85	19.698	< .001	0.568	1 < 4, 5, 6 2 < 4, 5, 6 3 < 4, 5, 6
Post-op 1st week (2)	6.94	4.85				
Post-op 1st month (3)	6.13	4.33				
Post-op 2nd month (4)	5.06	3.75				
Post-op 4th month (5)	4.69	3.67				
Post-op 1st year (6)	4.50	3.74				

ASIA Motor Scores

Figure 5 illustrates the changes in ASIA Motor Scores from pre-intervention to post-intervention assessments. A steady increase in ASIA Motor Scores was observed starting from the first week after MSCdE treatment, indicating progressive motor function improvement.

Figure 5. Changes observed in the pre-test and post-test means of the patients' Asia Motor Score values.

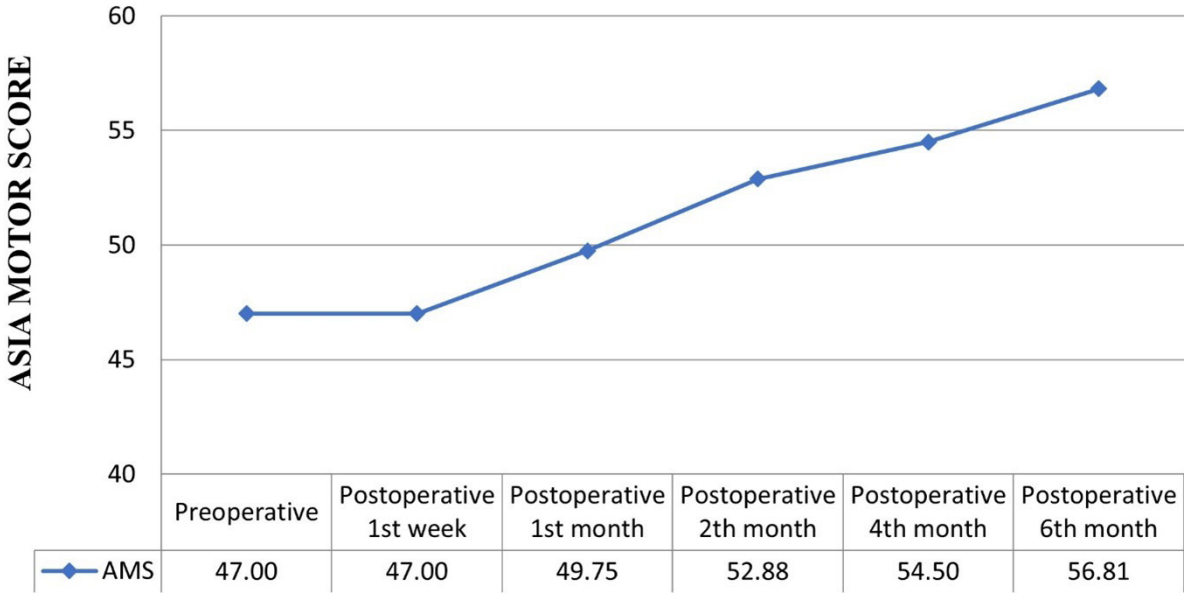


Table 5 summarizes the repeated-measures ANOVA results for ASIA Motor Scores. The analysis revealed a statistically significant improvement in scores (F=41.098, p<0.001). Post-hoc Bonferroni testing showed that pre-test and 1-week post-test scores were significantly lower than scores at 1 month, 2 months, 4 months, and 6 months. Furthermore, significant differences were observed between 1-month and later assessments (2 months, 4 months, and 6 months), with the most substantial improvement noted by 6 months.

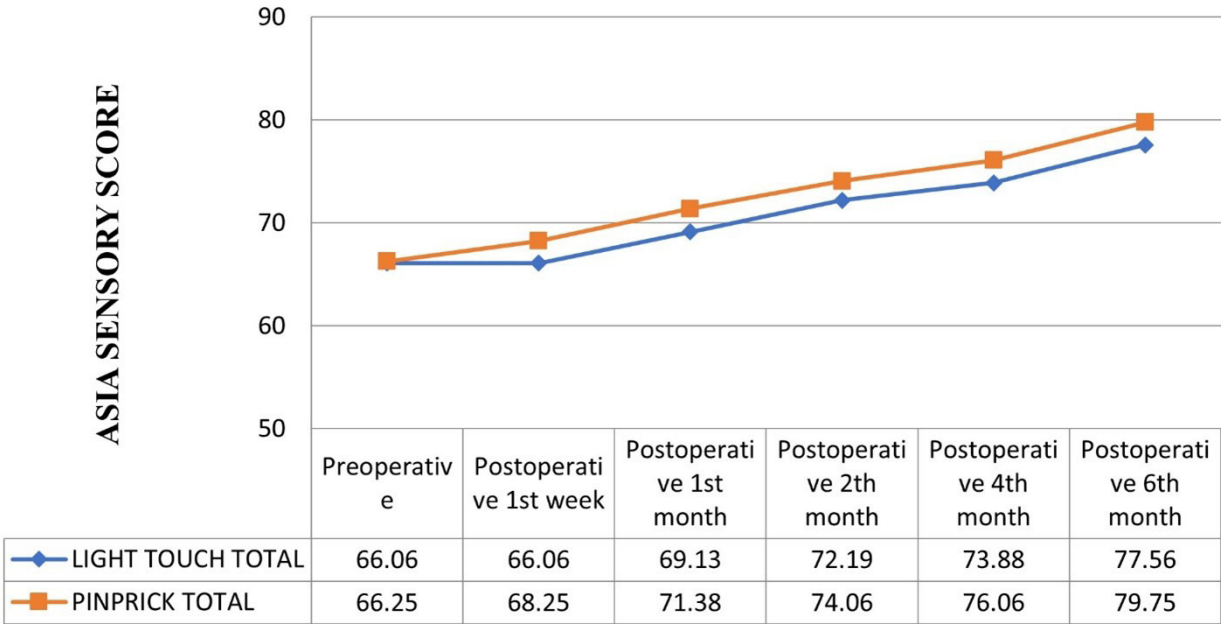
Table 5. Repeated measures ANOVA results for changes in patients' Asia Motor Score values before and after the intervention.

Time	Mean	SD	F	p	η^2_p	post-hoc
Pre-op (1)	47.000	21.153	41.098	< .001	0.733	1 < 3, 4, 5, 6 2 < 3, 4, 5, 6 3 < 4, 5, 6 4 < 6
Post-op 1st week (2)	47.000	21.153				
Post-op 1st month (3)	49.750	19.784				
Post-op 2nd month (4)	52.875	19.568				
Post-op 4th month (5)	54.500	19.343				
Post-op 1st year (6)	56.813	18.738				

ASIA Sensory Scores

Figure 6 depicts the changes in ASIA Sensory Scores for Light Touch (LT) and Pinprick (PP) sensations. A general increase in both sensory scores was observed following the MSCdE intervention.

Figure 6. Changes observed in the pre-test and post-test means of the patients' Asia Sensory Score values



	Preoperative	Postoperative 1st week	Postoperative 1st month	Postoperative 2th month	Postoperative 4th month	Postoperative 6th month
LIGHT TOUCH TOTAL	66.06	66.06	69.13	72.19	73.88	77.56
PINPRICK TOTAL	66.25	68.25	71.38	74.06	76.06	79.75

Table 6 presents the repeated-measures ANOVA results for ASIA Sensory LT scores, indicating a statistically significant improvement ($F=9.571$, $p<0.001$). Post-hoc Bonferroni testing revealed that pre-test, 1-week post-test, and 1-month post-test scores were significantly lower than scores obtained at 4 months and 6 months, demonstrating a progressive improvement in sensory function.

Table 6. Repeated measures ANOVA results for changes observed in Asia Sensory Score - LT values of patients before and after the intervention.

Time	Mean	SD	F	p	η^2_p	post-hoc
Pre-op (1)	66.063	21.306	9.571	< .001	0.390	1 < 5, 6 2 < 5, 6 3 < 5, 6
Post-op 1st week (2)	66.063	21.306				
Post-op 1st month (3)	69.125	19.893				
Post-op 2nd month (4)	72.188	19.170				
Post-op 4th month (5)	73.875	19.328				
Post-op 1st year (6)	77.563	20.136				

Table 7 provides the results for ASIA Sensory PP scores. The analysis showed a statistically significant difference ($F=10.883$, $p<0.001$), with significant improvements observed at 2 months, 4 months, and 6 months compared to pre-test and 1-week post-test scores. Additionally, the 1-month post-test scores were significantly lower than those at 6 months, indicating ongoing sensory recovery.

Table 7. Repeated measures ANOVA results for changes observed in Asia Sensory Score - PP values of patients before and after the intervention.

Time	Mean	SD	F	p	η^2p	post-hoc
Pre-op (1)	66.250	21.227	10.883	< .001	0.420	1 < 4, 5, 6 2 < 4, 5, 6 3 < 6
Post-op 1st week (2)	68.250	19.797				
Post-op 1st month (3)	71.375	19.674				
Post-op 2nd month (4)	74.063	19.178				
Post-op 4th month (5)	76.063	19.468				
Post-op 1st year (6)	79.750	20.237				

Incontinence Scores (WIS and SFQ)

Figure 7 provides a graphical representation of the changes in Wexner Incontinence Score (WIS) and Qualiveen Short Form (SFQ) scores observed before and after MSCdE treatment. The figure highlights a notable decrease in both WIS and SFQ scores following the administration of MSCdE, suggesting significant improvement in both urinary and fecal incontinence.

Figure 7. Changes observed in the pre-test and post-test means of the patients' Wexner Incontinance Score and SF-Qualiveen values

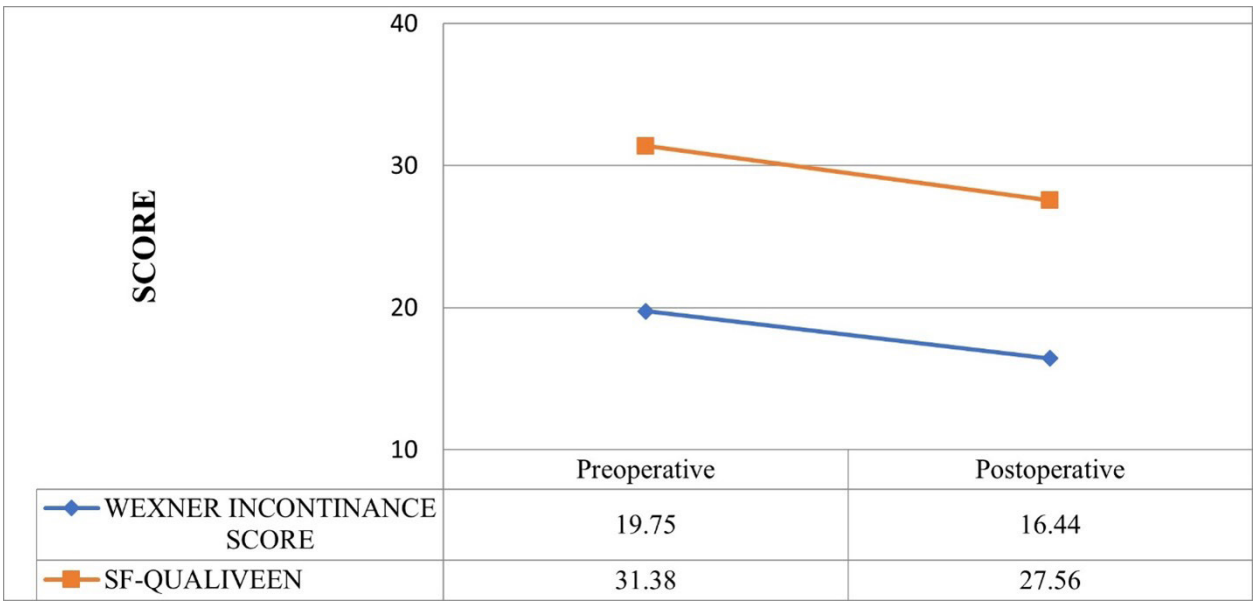


Table 8 summarizes the results of the paired samples t-test conducted to evaluate the statistical significance of the observed changes in WIS and SFQ scores. The analysis revealed statistically significant reductions for both measures. For the Wexner Incontinence Score (WIS), the t-test produced a t-value of 6.072 with a p-value less than 0.001, indicating a substantial decrease in fecal incontinence severity.

Table 8. Results of the t-test in paired samples regarding the changes observed in the Wexner Incontinence Score and SF-Qualiveen values of the patients before and after the intervention.

	n	Mean	SD	t	p	Cohen's d
WIS pre-op	16	19,75	0,68	6,072	< .001	1,52
WIS post-op 1st year	16	16,44	2,68			
SF pre-op	16	31,38	1,75	5,02	< .001	1,26
SF post-op 1st year	16	27,56	4,35			

Similarly, for the Qualiveen Short Form (SFQ), which assesses the impact of urinary incontinence on quality of life, the paired samples t-test yielded a t-value of 5.02 with a p-value less than 0.001. This result underscores a significant reduction in urinary incontinence.

DISCUSSION

This study provides robust evidence supporting the safety and efficacy of mesenchymal stem cell-derived exosome (MSC-dE) therapy for treating traumatic spinal cord injury (SCI). The results show significant improvements in neurological function, spasticity, and quality of life, aligning with recent literature. Additionally, MSC-dE therapy demonstrates a favorable safety profile.

Improvements in Neurological Function and Spasticity

Our findings indicate substantial enhancements in key outcome measures following MSC-dE treatment. Functional Independence Measure (FIM) motor scores increased significantly from 26.75 ± 9.81 to 43.88 ± 17.01 ($p<0.01$), reflecting improved motor

function. Similarly, ASIA motor scores rose from 47.00 ± 21.15 to 56.00 ± 18.74 ($p<0.001$), and ASIA sensory scores also showed significant gains. These results are consistent with previous studies that highlight the neuroprotective and regenerative potential of MSC-dE in SCI models [23,24].

The reduction in spasticity, as measured by the Modified Ashworth Scale (MAS), further supports the therapeutic benefits of MSC-dE. The MAS scores decreased from 7.00/6.94 to 4.56/4.50 ($p<0.001$), indicating alleviation of muscle spasticity. This finding aligns with similar studies and suggests that MSC-dE may modulate spasticity through mechanisms such as inflammation modulation and neuroprotection [25].

Quality of Life Improvements

Significant improvements were also observed in quality of life, with reductions in urinary and intestinal incontinence scores (Wexner Incontinence Score and Qualiveen Short Form). These reductions reflect a marked improvement in both urinary and fecal incontinence, addressing a major quality-of-life issue for SCI patients [26-27]. The MSC-dE therapy appears effective not only in improving neurological function but also in managing secondary complications associated with SCI.

Safety Profile

The safety profile of MSC-dE therapy was favorable, with minor side effects such as subfebrile fever, moderate headache, and muscle soreness, all classified as CTCAE v5.0 Grade 1. No serious adverse events were reported, aligning with safety findings from other MSC-dE studies [25,28].

Our findings are consistent with those of Khlaghpasand et al. (2024), which also reported significant improvements in neurological function and quality of life following MSC-dE therapy [25]. Both studies observed favorable safety outcomes and enhancements in motor and sensory functions. However, our study included a broader range of outcome measures, allowing for a more comprehensive assessment of functional recovery and spasticity. Khlaghpasand et al. focused on specific clinical outcomes, which may limit direct comparability. Despite this, both studies reinforce the evidence supporting MSC-dE therapy as a promising option for improving SCI outcomes and highlight the need for further research.

LIMITATIONS

Despite promising results, the study has limitations. The small sample size of 16 patients may limit generalizability. Larger studies are needed to confirm MSC-dE therapy's efficacy and safety. The Phase I design lacked randomization and a control group, making it difficult to attribute improvements solely to MSC-dE therapy. Although the one-year follow-up provides valuable insights, longer-term studies are required to assess the durability of treatment effects and any potential late-onset side effects. Variability in injury levels among patients may also affect outcomes, suggesting that stratified analyses could offer more tailored insights.

CONCLUSION

In conclusion, this Phase I study provides initial evidence that MSC-dE therapy is both safe and effective in improving neurological function, reducing spasticity, and enhancing quality of life in SCI patients. The observed benefits and favorable safety profile support MSC-dE as a promising therapeutic option for SCI. Further research with larger sample sizes, extended follow-up, and controlled study designs is necessary to validate these findings and establish MSC-dE therapy as a standard treatment for SCI.

Core Tip

Mesenchymal stem cell-derived exosomes (MSCdE) offer a novel therapeutic strategy for the treatment of spinal cord injury (SCI), targeting both neurological deficits and functional disabilities. This study establishes the safety and therapeutic efficacy of MSCdE, demonstrating significant improvements in motor function, sensory perception, spasticity, and urinary and bowel incontinence. The treatment protocol, which involves both intrathecal and intramuscular administration over 4.5 months, followed by a 1-year follow-up, highlights the potential of MSCdE in the clinical management of SCI. These results provide a strong rationale for further randomized controlled trials to validate the clinical efficacy of MSCdE in SCI therapy.

Author Contributions

Concept – Kabataş S; Civelek E; Design –Kabataş S, Savrunlu EC, Supervision – Kabataş S, Civelek E; Analysis and/or Interpretation – Civelek E, Kabataş S, Savrunlu EC, Kaplan N, Küçükçakır N; Literature Search –Kabataş S, Civelek E, Savrunlu EC, Boyalı O, Bozkurt M; Writing – Civelek E, Kabataş S, Kaplan N, Savrunlu EC, Boyalı O, Karaoz E, Kaplan N, Bozkurt M; Critical Reviews – Civelek E, Kabatas S

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Declaration of Conflicting Interests

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Statement of Human and Animal Rights

This article contains human subject and does not contain any conflict with the Helsinki Declaration.

Statement of Informed Consent

There is human subject in this article and written informed consents were obtained from the patient for their anonymized information to be published in this article and before the stem cell therapies.

Institutional Review Board Statement

The present study was approved by the local medical ethics committee (protocol number: 22122023.1).

Data Sharing Statement

No additional data are available.

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