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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells* (*WJSC*, *World J Stem Cells*) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, *etc*.

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ORIGINAL ARTICLE

Clinical Trials Study

Safety and efficiency of Wharton's Jelly-derived mesenchymal stem cell administration in patients with traumatic brain injury: First results of a phase I study

Serdar Kabatas, Erdinç Civelek, Osman Boyalı, Gülseli Berivan Sezen, Omer Ozdemir, Yeliz Bahar-Ozdemir, Necati Kaplan, Eyüp Can Savrunlu, Erdal Karaöz

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Abstract

BACKGROUND

Traumatic brain injury (TBI) is characterized by a disruption in the normal function of the brain due to an injury following a trauma, which can potentially cause severe physical, cognitive, and emotional impairment. Stem cell transplantation has evolved as a novel treatment modality in the management of TBI, as it has the potential to arrest the degeneration and promote regeneration of new cells in the brain. Wharton's Jelly-derived mesenchymal stem cells (WJ-MSCs) have recently shown beneficial effects in the functional recovery of neurological deficits.

AIM

To evaluate the safety and efficiency of MSC therapy in TBI.

METHODS

We present 6 patients, 4 male and 2 female aged between 21 and 27 years who suffered a TBI. These 6 patients underwent 6 doses of intrathecal, intramuscular (i.m.) and intravenous transplantation of WJ-MSCs at a target dose of 1×10^6/kg for each application route. Spasticity was assessed using the Modified Ashworth scale (MAS), motor function according to the Medical Research Council Muscle Strength Scale, quality of life was assessed by the Functional Independence Measure (FIM) scale and Karnofsky Performance Status scale.

RESULTS

Our patients showed only early, transient complications, such as subfebrile fever, mild headache, and muscle pain due to i.m. injection, which resolved within 24 h. During the one year follow-up, no other safety issues or adverse events were reported. These 6 patients showed improvements in their cognitive abilities, muscle spasticity, muscle strength, performance scores and fine motor skills when compared before and after the intervention. MAS values, which we used to assess spasticity, were observed to statistically significantly decrease for both left and right sides ($P < 0.001$). The FIM scale includes both motor scores ($P < 0.05$) and cognitive scores ($P < 0.001$) and showed a significant increase in pretest posttest analyses. The difference observed in the participants' Karnofsky Performance Scale values pre and post the intervention was statistically significant ($P < 0.001$).

CONCLUSION

This study showed that cell transplantation has a safe, effective and promising future in the management of TBI.

Key Words: Traumatic brain injury; Wharton Jelly; Stem cell therapy; Transplantation; Mesenchymal stem cell

Core Tip: Traumatic brain injury (TBI) is a disease that particularly affects the young population and causes serious neurological deficits. Current treatment options do not provide the hoped-for improvement in patients. For this reason, many studies are being conducted on new treatment options for TBI. In our phase I study, we present data showing that mesenchymal stem cell applications can be a safe and effective treatment option in this patient group.

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INTRODUCTION

Traumatic brain injury (TBI) is characterized by a disruption in the normal function of the brain due to an injury following a trauma, which can potentially cause severe physical, cognitive, and emotional impairment[1]. TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force[2]. Overall, the annual incidence of TBI when emergency department visits, hospitalizations, and deaths are included is approximately 823 per 100000[3]. Annually, more than 50 million patients and their family members who care for them worldwide suffer from TBI[4]. TBI occurs most frequently in early childhood (0-4 years) and young adults (15-24 years)[5]. Its second peak occurs in the elderly (> 65 years of age)[5]. Generally, the two main causes of TBI are falls and motor vehicle accidents[6].

The pathogenesis of TBI develops due to primary damage and subsequent secondary damage, which can cause permanent or temporary neurological damage[1,5]. Primary damage is an external force directly exposed to brain tissue [1,5]. Secondary damage can occur minutes or days after primary damage and involves inflammatory, molecular, and chemical pathophysiological processes that cause further brain damage[1,5]. As a result, despite appropriate treatments due to primary and secondary damage, the final condition in some patients is brain compression and death.

Despite surgical and medical treatments, it is clear that new treatment methods are needed for TBI[7]. One of the new treatment methods is stem cell applications. It can be seen in the literature that various stem cell studies have been conducted in patients with TBI since 2001[8,9]. Clinical studies for TBI have used different cell sources for transplantation, including mesenchymal stem cells (MSCs)[10,11]. MSCs have the 'bystander effect' ability to repair injured brain tissue [12]. Among MSCs, Wharton jelly-derived MSCs (WJ-MSCs) have a number of advantages, such as their abundance, easy to obtain with minimal invasiveness, and readily cultured to a sufficient number for transplantation without ethical issues of allografting[13].

In a previous study, we investigated the safety and feasibility of employing both the triple route and multiple WJ-MSC implantations as part of a treatment strategy for a patient diagnosed with hypoxic-ischemic encephalopathy (HIE)[14]. Although there is no evidence in clinical studies showing the engraftment and viability of stem cells given by different routes, rat studies have shown that the use of multiple routes increases the viability of transplanted cells[15]. Here we present 6 patients, 4 male and 2 female aged between 21 and 27 years, who suffered a TBI due to a road traffic accident. They underwent intrathecal (i.t.), intramuscular (i.m.), and intravenous (i.v.) transplantations of WJ-MSCs; 6 months to 4 years post TBI to overcome the residual deficits due to injuries.

MATERIALS AND METHODS

This phase I study was a single center, prospective, longitudinal medical experiment. The study was conducted in the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital. The MSC trial was approved by the Turkish Ministry of Health (protocol number: 56733164-203-E.12.19). The patients' legal representatives were informed of the procedure, and written informed consent forms were obtained per the Helsinki Declaration. The general data collected before the experimental therapy consisted of age, gender, cause of the TBI, length of time since the TBI, previous medical treatments for the TBI, and past medical histories.

Medical history

The 4 male and 2 female patients suffered a TBI due to a road traffic accident (Table 1). One of the patients had undergone decompressive craniectomy and ventriculoperitoneal shunting procedures and a few months later his craniectomy bone flap was placed back on the skull. One of the patients had subdural hematoma drainage and ventriculoperitoneal shunting procedures. One of the patients had ventriculoperitoneal shunting procedures but after 2 years the current shunt appeared not to be working. It was changed to a lumbo-peritoneal shunt. One of the patients had several cranial procedures. In addition, 2 of the patients had no surgery after the accident. The patients were awake but unresponsive, tetraplegic with high degree muscle spasms and had no speech, no sphincter control and no sign of communication. They had been in rehabilitation programs for approximately 6 months to 4 years without much improvement. Botulinum toxin injections for muscle spasms had provided temporary relief. They had a decorticated posture with upper extremity hyperflexion and lower extremity extension. Their muscle tones were increased and they had tremendous difficulties with daily activities such as mobilization and bathing. These 6 patients were referred to our hospital for the MSC trial. MSC treatment was started 6 to 48 months after TBI (23.66 ± 13.7 months).

Enrollment criteria

In the phase I study, we enrolled patients with TBI confirmed by imaging studies [such as computed tomography (CT) scans and magnetic resonance imaging], neurological examinations, and neurophysiological assessments (including electroencephalography). We established specific exclusion criteria, which encompassed focal central nervous system lesions (such as neoplastic growths) and chronic diseases (such as systemic conditions) necessitating long-term pharmacotherapy. Additionally, patients with head trauma resulting from a penetrating knife or gunshot wound were excluded. Prior to treatment initiation, thorough evaluations were conducted by medical professionals in the neurosurgery and physical therapy and rehabilitation departments.

Procedure

Umbilical cords were sourced from LivMedCell's Good Manufacturing Practice facility in Istanbul, Turkey. These cords were generously donated by various individuals after obtaining informed consent, as sanctioned by LivMedCell's institutional regulatory board. Specifically, we procured postnatal umbilical cords from donors who had undergone full-term pregnancies. Our previous publications comprehensively detailed the entire process, including umbilical cord processing, quality control, characterization of WJ-MSCs *via* flow cytometry, cell differentiation, karyotyping, pre-transplantation procedures, and the surgical steps involved in WJ-MSC transplantation[14,16]. The i.t., i.m., and i.v. implantation procedure of WJ-MSCs was performed when the patient was stable, without contraindications for sedoanesthesia from the viewpoint of internal medicine, and in the absence of serious infectious diseases, including sepsis, immediately prior to the procedure (Table 2).

Clinical evaluation

Pre-treatment neurological examination: Before treatment, a comprehensive assessment was conducted by a multidisciplinary team of medical and rehabilitation specialists. Throughout the process, detailed evaluations of neurological function and overall functionality were meticulously documented. Spasticity levels were measured using the Modified Ashworth scale (MAS), while motor function was assessed using the Medical Research Council (MRC) Muscle Strength Scale. Additionally, quality of life was evaluated based on parental input, utilizing the Functional Independence Measure

Table 1 Study group characteristics

Characteristics		*n*	%
Age (yr)	21	1	16.7
	22	1	16.7
	25	2	33.3
	26	1	16.7
	27	1	16.7
Sex	Female	2	33.3
	Male	4	66.7
Cause of spinal cord injury	Traffic accident	6	100.0
Comorbidity	None	6	100.0
Treatments before transplantation	Non-surgical	2	33.3
	Decompressive craniectomy	1	16.7
	Acute subdural hematoma evacuation and ventriculoperitoneal shunt	1	16.7
	Decompressive craniectomy and ventriculoperitoneal shunt	1	16.7
	Ventriculoperitoneal shunt	1	16.7
Duration between spinal cord injury and first transplantation	6 months	1	16.7
	18 months	1	16.7
	22 months	1	16.7
	24 months	2	33.3
	48 months	1	16.7

(FIM) scale and the Karnofsky Performance Status scale.

Safety evaluation criteria: The safety parameters for the transplantation procedure encompassed vigilance for signs such as infection, fever, headache, pain, elevated C-reactive protein levels, increased leukocytosis, and potential allergic reactions or shocks. Additionally, perioperative complications, including anesthesia- and analgesia-related issues, as well as wound infections, were closely monitored during the 7-14 d following the procedure. For the utilization of WJ-MSCs, the safety criteria involved assessing infection risk, neuropathic pain, potential cancer development, and any adverse effects on neurological, cardiological, pulmonary, hematological, hepatic, and renal organ systems. This evaluation spanned a 1-year follow-up period.

Follow-up assessment of treatment success: The follow-up evaluations consisted of a neurological examination evaluating motor function according to the MRC Muscle Strength Scale. Spasticity was assessed using the MAS, and quality of life was assessed based on the functional recovery estimated by the FIM scale and Karnofsky Performance Status scale [17]. Furthermore, an assessment was conducted to monitor the occurrence of neuropathic pain, secondary infections, urinary tract infections, and skin pressure ulcers.

RESULTS

Safety and adverse events

Among the six patients, the procedures were well-tolerated, and no severe adverse events related to the injections were reported. Instead, our patients experienced only early and transient complications, including subfebrile fever, mild headaches, and muscle pain due to i.m. injection. Fortunately, these issues resolved within 24 h. Neuropathic pain, secondary infections, urinary tract infections, and pressure ulcers of the skin were not observed. During the one year follow-up period, no other safety issues or adverse events were reported. There was no evidence of infusion-related toxicity to cardiac, pulmonary, hematological, hepatic, renal, or neurological organ systems. There were no deaths.

FIM scale score

Remarkable enhancements in quality of life were noted, evaluated using the FIM scale, which encompasses both motor and cognitive assessments. Figure 1A shows the visual analysis of the changes observed in the pretest and posttest averages of the patients' FIM Motor and Cognitive Score values. While there was a continuous increase in the FIM Cognitive Score values of the patients after the intervention, there was a very small increase in the Motor Score values.

Table 2 Administration schedule

Date	Route	WJ-MSCs
Round 1		
	I.t.	1×10^6/kg (3 mL in total)
	I.v.	1×10^6/kg (30 mL in total)
	I.m.	1×10^6/kg (20 mL in total)
Round 2 (2nd wk)		
	I.t.	1×10^6/kg (3 mL in total)
	I.v.	1×10^6/kg (30 mL in total)
	I.m.	1×10^6/kg (20 mL in total)
Round 3 (1st month)		
	I.t.	1×10^6/kg (3 mL in total)
	I.v.	1×10^6/kg (30 mL in total)
	I.m.	1×10^6/kg (20 mL in total)
Round 4 (2nd month)		
	I.t.	1×10^6/kg (3 mL in total)
	I.v.	1×10^6/kg (30 mL in total)
	I.m.	1×10^6/kg (20 mL in total)
Round 5 (3rd month)		
	I.t.	1×10^6/kg (3 mL in total)
	I.v.	1×10^6/kg (30 mL in total)
	I.m.	1×10^6/kg (20 mL in total)
Round 6 (4th month)		
	I.t.	1×10^6/kg (3 mL in total)
	I.v.	1×10^6/kg (30 mL in total)
	I.m.	1×10^6/kg (20 mL in total)

I.t.: Intrathecal; I.v.: Intravenous; I.m.: Intramuscular; WJ-MSCs: Wharton's Jelly-derived mesenchymal stem cells.

Tables 3 and 4 show the Friedman Test Results of the changes observed in the FIM Motor Score values of the patients before and after the intervention. According to the analysis in Table 3, the differences observed in the FIM Motor Score values of the participants before and after the intervention were statistically significant (χ^2 = 14.310, P < 0.05). The Wilcoxon Signed Rank Test was performed between binary measurements to determine which variables showed differences. As a result of this analysis, differences were observed between preop and postop 1st wk (Z = 0.000, P = 1.00), postop 1st month (Z = -1.000, P = 0.317), postop 2nd month (Z = -1.604, P = 0.109), postop 4th month. There is no significant difference between (Z = -1.604, P = 0.109) and postoperative 12th months (Z = -1.604, P = 0.109).

Tables 5 and 6 show the Friedman Test Results of the changes observed in the FIM Cognitive Score values of the patients before and after the intervention. According to the analysis in Table 5, the differences observed in the participants' FIM Cognitive Score values before and after the intervention were statistically significant (χ^2 = 26.160, P < 0.001). The Wilcoxon Signed Rank Test was performed between binary measurements to determine which variables showed differences. As a result of this analysis, there was no significant difference between preoperative and postoperative 1st wk (Z = -1.342, P = 0.108); postop 1st month (Z = -2.060, P = 0.039), postop 2nd month (Z = -2.060, P = 0.039), postop 4th month (Z = -2.023, P = 0.043) and postop 12th month (Z = -2.214, P = 0.027) showed significant differences. Thus, while there was no significant difference in the FIM Cognitive Scores of the participants in the first week after the intervention, a significant increase was observed in the first month and thereafter.

Modified Ashworth and MRC muscle strength scale

MAS scores were similar on both sides. Figure 1B shows the visual analysis of the changes observed in the patients' MAS right and left values before and after the procedure. It was observed that there was a continuous decrease in the patients' MAS right and left values after the intervention. Tables 7 and 8 show the Friedman Test Results of the changes observed in the MAS right values of the patients before and after the intervention. According to the analysis in Table 7, the

Table 3 Friedman test results of the changes observed in the Functional Independence Measure Motor Score values of the patients before and after the intervention

	n	Mean	SD	Mean rank	χ^2	df	*P* value
Preoperative	6	13.17	0.41	2.67	14.310	5	0.014
Postoperative 1st wk	6	13.17	0.41	2.67			
Postoperative 1st month	6	13.33	0.82	2.92			
Postoperative 2nd month	6	14.17	1.60	4.08			
Postoperative 4th month	6	14.33	1.97	4.33			
Postoperative 1st yr	6	14.33	1.97	4.33			

Table 4 Functional Independence Measure Motor Score values of each patient

	FIM Scale, Motor Score: Self-care/Sphincter Control/Transfers/Locomotion					
	Pre-test	Post-test (1st wk)	Post-test (1st month)	Post-test (2nd month)	Post-test (4th month)	Post-test (12th month)
Patient 1	13	13	13	15	15	15
Patient 2	14	14	15	17	18	18
Patient 3	13	13	13	13	13	13
Patient 4	13	13	13	14	14	14
Patient 5	13	13	13	13	13	13
Patient 6	13	13	13	13	13	13

FIM: Functional Independence Measure.

Table 5 Friedman test results of the changes observed in the Functional Independence Measure Cognitive Score values of the patients before and after the intervention

	n	Mean	SD	Mean rank	χ^2	df	*P* value
Preoperative	6	5.67	1.63	1.58	26.160	5	0.000
Postoperative 1st wk	6	6.50	1.76	2.08			
Postoperative 1st month	6	7.67	2.42	2.92			
Postoperative 2nd month	6	8.83	3.49	3.75			
Postoperative 6th month	6	11.00	4.43	4.92			
Postoperative 1st yr	6	11.83	3.97	5.75			

differences observed in the MAS right values of the participants before and after the intervention were statistically significant (χ^2 = 28.641, P < 0.001). The Wilcoxon Signed Rank Test was performed between binary measurements to determine which variables showed differences. As a result of this analysis, there was no significant difference between preoperative and postoperative 1st wk (Z = -1.000, P = 0.317); postop 1st month (Z = -2.264, P = 0.024), postop 2nd month (Z = -2.214, P = 0.027), postop 4th month (Z = -2.226, P = 0.026) and postop 12th month (Z = -2.214, P = 0.027), showed significant differences. Thus, while there was no significant difference in the participants' MAS right scores in the first week after the intervention, a significant decrease was observed in the first month and thereafter.

Tables 9 and 10 show the Friedman Test Results of the changes observed in the MAS left values of the patients before and after the intervention. According to the analysis in Table 9, the differences observed in the MAS left values of the participants before and after the intervention were statistically significant (χ^2 = 28.462, P < 0.001). The Wilcoxon Signed Rank Test was performed between binary measurements to determine which variables showed differences. As a result of this analysis, there was no significant difference between pre-test and post-test 1st wk (Z = -1.000, P = 0.317); post-test 1st month (Z = -2.226, P = 0.026), post-test 2nd month (Z = -2.232, P = 0.026), post-test 4th month (Z = -2.214, P = 0.027) showed significant differences compared with post-test 12th month (Z = -2.207, P = 0.027). Thus, while there was no significant difference in the participants' MAS left scores in the first week after the intervention, a significant decrease was observed in the first month and thereafter.

Table 6 Functional Independence Measure Cognitive Score values of each patient

	FIM Scale, Cognitive Score: Communication/Social Cognition (TS:35)					
	Pre-test	Post-test (1st wk)	Post-test (1st month)	Post-test (2nd month)	Post-test (4th month)	Post-test (12th month)
Patient 1	5	5	8	9	11	11
Patient 2	9	9	12	15	17	18
Patient 3	5	5	6	6	8	8
Patient 4	5	7	7	9	15	15
Patient 5	5	8	8	9	10	11
Patient 6	5	5	5	5	5	8

FIM: Functional Independence Measure.

Table 7 Friedman test results of the changes observed in the Modified Ashworth Score right values of the patients before and after the intervention

	n	Mean	SD	Mean rank	χ^2	df	*P* value
Preoperative	6	19.83	4.58	5.58	28.641	5	0.000
Postoperative 1st wk	6	19.50	4.46	5.33			
Postoperative 1st month	6	17.33	4.68	4.00			
Postoperative 2nd month	6	16.17	5.35	2.83			
Postoperative 4th month	6	15.17	4.99	1.83			
Postoperative 1st yr	6	13.83	4.83	1.42			

Table 8 Modified Ashworth Score right values of each patient

	Modified Ashworth Score (right)					
	Pre-test	Post-test (1st wk)	Post-test (1st month)	Post-test (2nd month)	Post-test (4th month)	Post-test (12th month)
Patient 1	19	19	16	14	12	12
Patient 2	20	20	16	15	14	14
Patient 3	20	20	18	17	16	11
Patient 4	26	26	24	24	22	22
Patient 5	12	12	10	8	8	8
Patient 6	22	20	20	19	19	16

Figure 2 shows the visual analysis of the changes observed in the preoperative and postoperative averages of the MRC Muscle Strength Scale right and left values in the patients. It was observed that there was a general increase, albeit small, in the MRC Muscle Strength Scale right and left values of the patients after the intervention. Tables 11 and 12 show the Friedman Test Results of the changes observed in the MRC Muscle Strength Scale right values of the patients before and after the intervention. Table 11 shows the Friedman Test Results of the changes observed in the MRC Muscle Strength Scale right values of the patients before and after the intervention (χ^2 = 13.214, P < 0.05). The Wilcoxon Signed Rank Test was performed between binary measurements to determine which variables showed differences. As a result of this analysis, differences were observed between pre-test and post-test 1st wk (Z = 0.000, P = 1.000), post-test 1st month (Z = -1.414, P = 0.157), post-test 2nd month (Z = -1.633, P = 0.102), post-test 4th month (Z = -1.633, P = 0.102) and post-test 12th month (Z = -1.633, P = 0.102).

Tables 13 and 14 show the Friedman Test Results of the changes observed in the MRC Muscle Strength Scale left values in the patients before and after the intervention. According to the analysis in Table 13, the differences observed in the MRC Muscle Strength Scale left values of the participants before and after the intervention were statistically significant (χ^2 = 13.506, P < 0.05). The Wilcoxon Signed Rank Test was performed between binary measurements to determine which variables showed differences. As a result of this analysis, pre-test and post-test 1st wk (Z = 0.000, P = 1.000), post-test 1st month (Z = -1.414, P = 0.157), post-test 2nd month (Z = -1.633), P = 0.102), post-test 4th month (Z = -1.633, P = 0.102) and

Table 9 Friedman test results of the changes observed in the Modified Ashworth Score left values of the patients before and after the intervention

	n	Mean	SD	Mean rank	χ^2	df	*P* value
Preoperative	6	18.83	5.04	5.58	28.462	5	0.000
Postoperative 1st wk	6	18.50	4.85	5.25			
Postoperative 1st month	6	16.33	4.68	3.83			
Postoperative 2nd month	6	15.83	5.04	3.25			
Postoperative 4th month	6	14.33	4.18	1.83			
Postoperative 1st yr	6	13.00	4.60	1.25			

Table 10 Modified Ashworth Score left values of each patient

	Modified Ashworth Score (left)					
	Pre-test	Post-test (1st wk)	Post-test (1st month)	Post-test (2nd month)	Post-test (4th month)	Post-test (12th month)
Patient 1	19	19	16	16	14	12
Patient 2	20	20	15	14	13	13
Patient 3	20	20	18	17	16	11
Patient 4	23	23	21	21	19	19
Patient 5	9	9	8	7	7	6
Patient 6	22	20	20	20	17	17

Table 11 Friedman test results of the changes observed in the Medical Research Council muscle strength scale right values of the patients before and after the intervention

	n	Mean	SD	Mean rank	χ^2	df	*P* value
Preoperative	6	3.33	1.86	2.58	13.214	5	0.021
Postoperative 1st wk	6	3.33	1.86	2.58			
Postoperative 1st month	6	3.67	1.51	3.33			
Postoperative 2nd month	6	4.00	1.10	4.00			
Postoperative 4th month	6	4.17	0.98	4.25			
Postoperative 1st yr	6	4.17	0.98	4.25			

post-test 12th month showed differences (Z = -1.633, P = 0.102).

Karnofsky Performance Status scale

The Karnofsky Performance Score (KPS) ranking runs from 100 to 0, where 100 is "perfect" health and 0 is death. Figure 3 shows the visual analysis of the changes observed in the pretest and posttest averages of the patients' KPS values. It was observed that there was a general increase in the KPS values of the patients after the intervention. Tables 15 and 16 show the Friedman Test Results of the changes observed in the KPS values of the patients before and after the intervention. According to the analysis in Table 15, the differences observed in the KPS values of the participants before and after the intervention were statistically significant (χ^2 = 27.557, P < 0.001). The Wilcoxon Signed Rank Test was performed between binary measurements to determine which variables showed differences. As a result of this analysis, pre-test and post-test 1 wk (Z = 0.000, P = 1.000), post-test 1st month (Z = -1.633, P = 0.102) and post-test 2nd month (Z = -1.890, P = 0.059) showed no significant differences; however, there was a significant difference between post-test 4th month (Z = -2.232, P = 0.026) and post-test 12th month (Z = -2.232, P = 0.026). Thus, while there was no significant difference in the KPS scores of the participants until the 2nd month after the intervention, a significant decrease was observed at the 4th month and later.

Table 12 Medical Research Council muscle strength scale right values of each patient

	MRC muscle strength scale (right)					
	Pre-test	Post-test (1st wk)	Post-test (1st month)	Post-test (2nd month)	Post-test (4th month)	Post-test (12th month)
Patient 1	2	2	2	3	3	3
Patient 2	2	2	3	3	3	3
Patient 3	5	5	5	5	5	5
Patient 4	1	1	2	3	4	4
Patient 5	5	5	5	5	5	5
Patient 6	5	5	5	5	5	5

MRC: Medical Research Council.

Table 13 Friedman test results of the changes observed in the Medical Research Council muscle strength scale left values of the patients before and after the intervention

	n	Mean	SD	Mean rank	χ^2	df	*P* value
Preoperative	6	3.33	1.86	2.58	13.506	5	0.019
Postoperative 1st wk	6	3.33	1.86	2.58			
Postoperative 1st month	6	3.67	1.51	3.25			
Postoperative 2nd month	6	4.00	1.10	4.08			
Postoperative 4th month	6	4.00	1.10	4.08			
Postoperative 1st yr	6	4.17	0.98	4.42			

Table 14 Medical Research Council muscle strength scale left values of each patient

	MRC muscle strength scale (left)					
	Pre-test	Post-test (1st wk)	Post-test (1st month)	Post-test (2nd month)	Post-test (4th month)	Post-test (12th month)
Patient 1	2	2	2	3	3	3
Patient 2	2	2	3	3	3	4
Patient 3	5	5	5	5	5	5
Patient 4	1	1	2	3	3	3
Patient 5	5	5	5	5	5	5
Patient 6	5	5	5	5	5	5

MRC: Medical Research Council.

DISCUSSION

Following TBI, cerebral damage leads to ischemia, triggering anaerobic glycolysis. This process results in the degeneration of vascular and cellular structures within the cerebral tissue, ultimately causing necrosis and apoptosis[18]. While decompressive craniotomy and pharmacological treatments are commonly proposed for TBI management, they do not fully halt disease progression[19,20]. However, cell transplantation offers the potential to alter the course of the disease. Stem cells, with their ability to differentiate and self-renew into mature, multipotent cells, play a crucial role[21]. In cases of TBI, where diffuse axonal injury disrupts the myelin sheath and affects neurotransmission, stem cells migrate to the injury site, mediating inflammatory markers and reducing inflammation. These cells also differentiate into neural cells and oligodendrocytes, promoting remyelination of damaged axons and enhancing neural pathways[22,23]. Additionally, stem cells secrete factors such as brain-derived neurotrophic factor, contributing to neuroprotection and neuroangiogenesis[24]. Furthermore, MSCs have the ability to modulate inflammation-associated immune cells and cytokines in TBI-induced cerebral inflammatory responses[22]. This offers a new insight into the mechanisms responsible for the immunomodulatory effect of MSC transplantation, with implications for functional neurological recovery after TBI[22].

Table 15 Friedman test results of the changes observed in the Karnofsky performance scale values of the patients before and after the intervention

	n	Mean	SD	Mean rank	χ^2	df	*P* value
Preoperative	6	15.00	5.48	1.92	27.557	5	0.000
Postoperative 1st wk	6	15.00	5.48	1.92			
Postoperative 1st month	6	21.67	11.69	2.92			
Postoperative 2nd month	6	23.33	12.11	3.25			
Postoperative 4th month	6	33.33	12.11	5.33			
Postoperative 1st yr	6	36.67	15.06	5.67			

Table 16 Karnofsky performance scale values of each patient

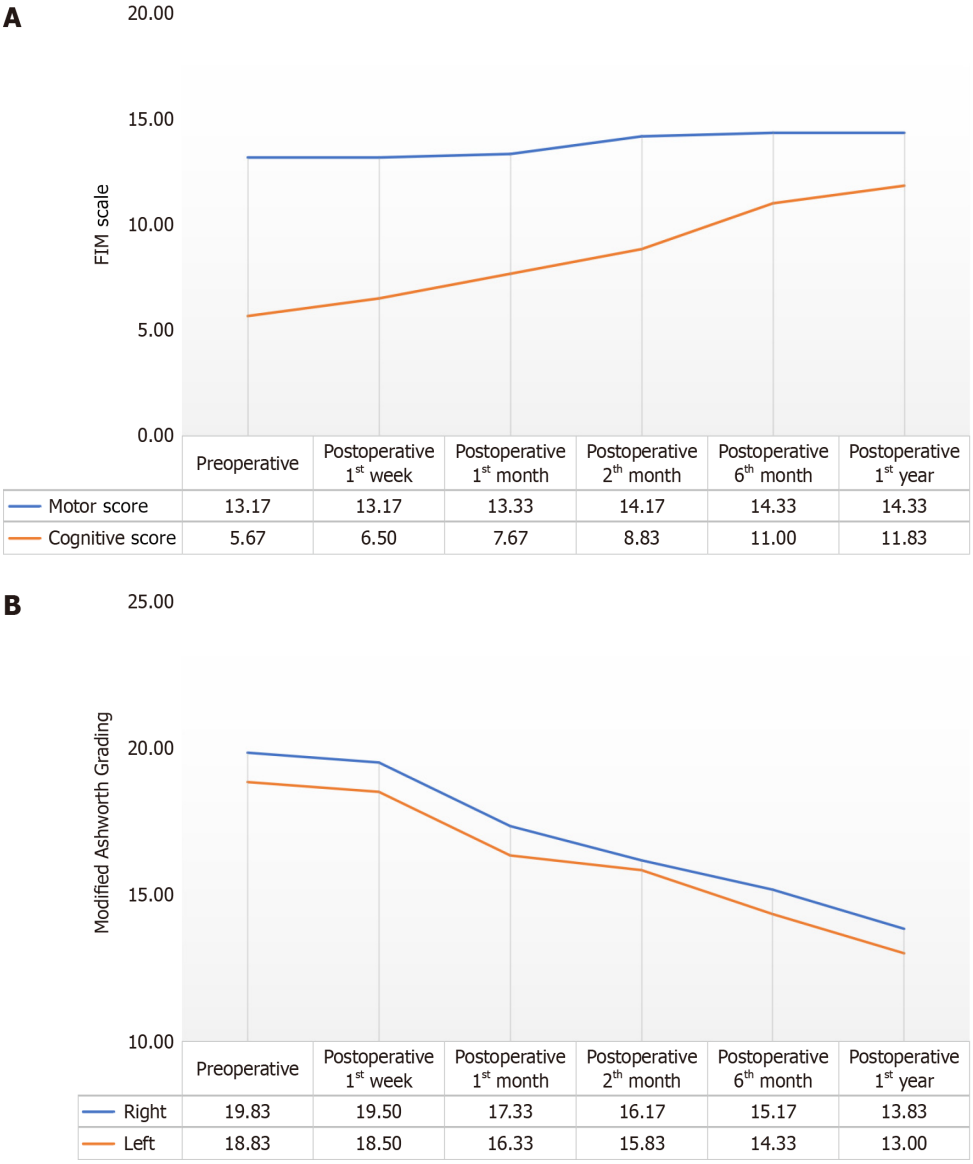
	Karnofsky performance scale					
	Pre-test	Post-test (1st wk)	Post-test (1st month)	Post-test (2nd month)	Post-test (4th month)	Post-test (12th month)
Patient 1	10	10	20	20	30	30
Patient 2	20	20	40	40	50	50
Patient 3	20	20	20	30	40	50
Patient 4	20	20	30	30	40	50
Patient 5	10	10	10	10	20	20
Patient 6	10	10	10	10	20	20

Preclinical studies have explored various stem cell types and administration routes, suggesting that cell transplantation may improve functional outcomes in TBI patients.

In this study, we administered both triple route (i.v., i.t., i.m.) and multiple WJ-MSCs to 6 patients. WJ represents a rich source of stem cells used in several animal models of NeDs. WJ-MSCs were used as they are safe and can be easily isolated. WJ-MSCs express higher levels of HLA-G, which has an immunosuppressive effect on natural killer cells and T cells[14]. This expression profile plays an important role in avoiding maternal immunity against the fetus during pregnancy and provides better graft acceptance[14]. HLA-G secretion makes WJ-MSCs an ideal cell source for third-party/allogeneic applications. According to recent clinical trials, WJ-MSC treatment has promising effects on patients with NeDs like TBI[14].

Numerous global clinical studies have explored the safety and efficacy of cellular therapy for TBI[1,12,25]. However, the choice of the targeted route for stem cell transplantation is crucial. Achieving a higher concentration of stem cells in the specific target area is essential to maximize the benefits of cellular transplantation. Therefore, regional routes for cell transplantation should be carefully considered[24]. In TBI cases, intracerebral transplantation appears to be the ideal targeted route, but it involves an invasive procedure that may cause secondary damage to cerebral tissue. I.t. delivery of stem cells, on the other hand, has several advantages. It enhances neural connectivity, reduces pro-inflammatory mediators in the brain and spinal cord, and promotes migration and differentiation of neuronal precursors[18]. Notably, Sharma *et al*[23] propose that i.t. transplantation of autologous bone marrow mononuclear cells contribute to functional recovery from neurological deficits, ultimately improving the quality of life in chronic TBI patients. On the other hand, various studies have shown that i.v. transplantation alone can be sufficient in terms of effectiveness in the treatment of TBI[24,26,27]. However, i.v. transplantation could potentially trap delivered cells in the lungs, and the total number of cells reaching the target area may not be sufficient to yield desirable results in TBI cases[28]. In a previous study, we documented the safety and viability of employing both the triple-route and multiple WJ-MSC implantations for treating patients with HIE and cerebral palsy[14]. In this pilot study, 6 patients underwent WJ-MSCs with the combined (i.t., i.v. and i.m.) approach for 6 months. We consider these routes to be minimally invasive and to target the desired area.

In the current study, patients showed improvements in speech, cognitive abilities, attention span, concentration, recent memories, fine and gross motor activities[14]. Posttraumatic hydrocephalus (PTH) affects 11.9%-36% of patients undergoing decompressive craniectomy and is an important cause of morbidity after TBI[29]. Hydrocephalus often develops more than a month after a patient undergoes decompressive craniectomy and can be associated with poorer outcomes. Early diagnosis and treatment of PTH (ventriculoperitoneal shunting, *etc.*) can prevent further neurological compromise in patients who are recovering from TBI[30]. When the entire literature was scanned, we could not find any literature regarding the effect of stem cells on hydrocephalus. However logically, it can be assumed that the stem cells will increase intracranial hypertension. As shown in cranial CT follow-up, this did not occur in our study. There was no need to make any changes in the adjustable shunt pressure of the patient during the follow-up process. Thus, this provides evidence that stem cell therapy does not directly affect the development of hydrocephalus.



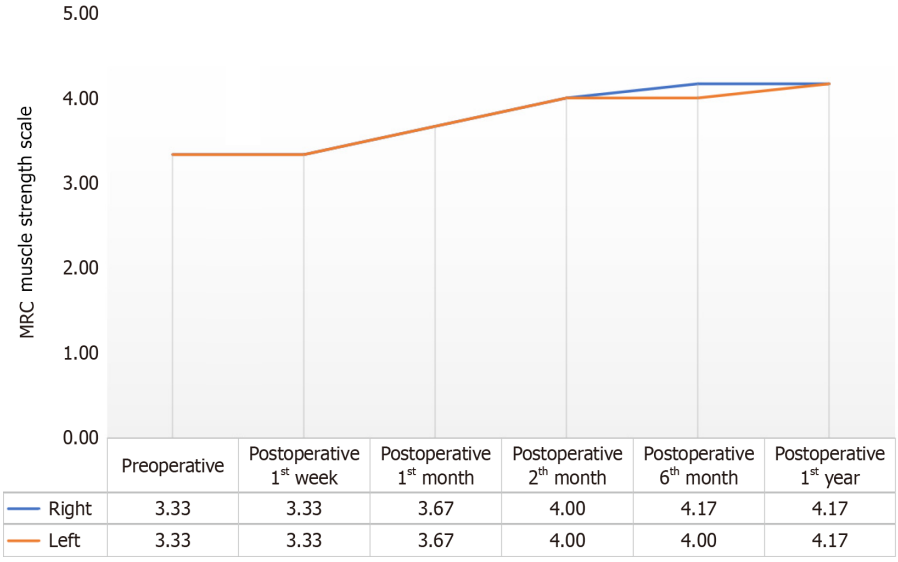
	Preoperative	Postoperative 1st week	Postoperative 1st month	Postoperative 2th month	Postoperative 6th month	Postoperative 1st year
Motor score	13.17	13.17	13.33	14.17	14.33	14.33
Cognitive score	5.67	6.50	7.67	8.83	11.00	11.83

	Preoperative	Postoperative 1st week	Postoperative 1st month	Postoperative 2th month	Postoperative 6th month	Postoperative 1st year
Right	19.83	19.50	17.33	16.17	15.17	13.83
Left	18.83	18.50	16.33	15.83	14.33	13.00

Figure 1 The changes observed in the patients' average scores of Functional Independence Measure Motor and Cognitive Score values and Modified Ashworth Score right and left values before the procedure, 1st wk after the procedure, and at the 1st month, 2nd month, 6th month and 1st year. A: The changes observed in the patients' average scores of Functional Independence Measure Motor and Cognitive Score values before the procedure, 1st wk after the procedure, and at the 1st month, 2nd month, 6th month and 1st year; B: The changes observed in the patients' average scores of Modified Ashworth Score right and left values before the procedure, 1st wk after the procedure, and at the 1st month, 2nd month, 6th month and 1st year. FIM: Functional Independence Measure.

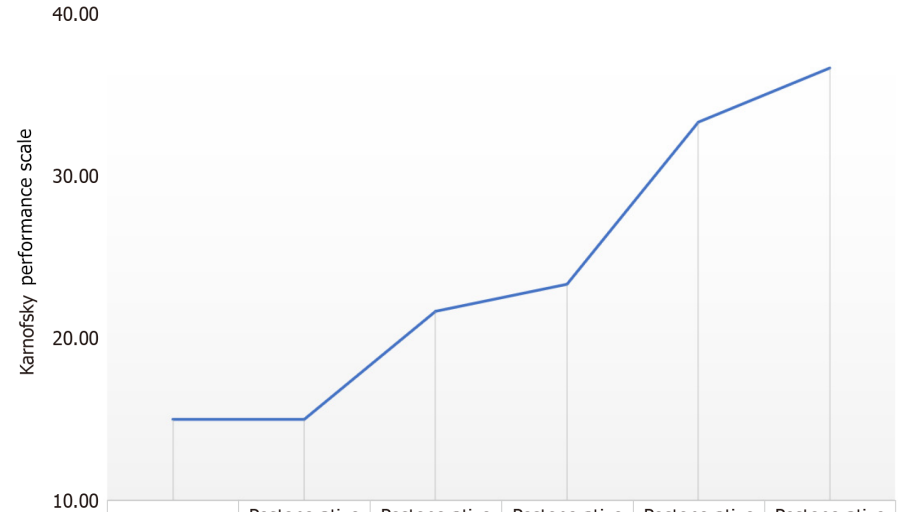
Spasticity makes daily life very difficult. Spasticity symptoms include increased muscle tone (hypertonicity), muscle spasms, shearing, increased deep tendon reflexes, and clonus[31]. The degree of spasticity varies from mild muscle stiffness to painful, severe uncontrollable muscle spasms[31]. The effectiveness of pharmacological agents or rehabilitation in the treatment of spasticity is limited according to studies in the literature[32-33]. Significant improvement was observed in our study. In addition, treatments such as rehabilitation or baclofen last for many years or even a lifetime in multiple sessions. This always creates problems in transferring patients to the hospital. Similarly, existing conventional treatments provide limited success in improving cognitive dysfunction, motor dysfunction and quality of life[36-39]. However, in our patients, both cognitive functions, motor dysfunction and quality of life improved significantly. However, we think that it is necessary to increase the number of patients in this study with larger-scale studies.

Due to the design of our study, we did not include a control group with which we could compare the natural healing process. However, when the studies in the literature were evaluated, we chose our patient group among those in whom natural recovery was not expected. The time between participants' TBI and receiving stem cell treatment was between 6 and 48 months. All patients participating in the study were in a vegetative state and did not show significant functional improvement. Previous studies have shown that there is an almost 4-fold increase in functional scores, especially in severe TBI patients, within the first 3 months, but the natural recovery rate decreases significantly after 3 months[40,41]. In the study conducted by Katz *et al*[42], it was reported that spontaneous recovery was seen in most of their patients within the first 3 months[42]. The fact that our patients did not achieve significant functional improvement in the first 6



	Preoperative	Postoperative 1st week	Postoperative 1st month	Postoperative 2th month	Postoperative 6th month	Postoperative 1st year
Right	3.33	3.33	3.67	4.00	4.17	4.17
Left	3.33	3.33	3.67	4.00	4.00	4.17

Figure 2 The changes observed in the average scores of the patients before the procedure, at the 1st wk, 1st month, 2nd month, 6th month and 1st year after the procedure, regarding the Medical Research Council muscle strength scale right and left values. MRC: Medical Research Council.



	Preoperative	Postoperative 1st week	Postoperative 1st month	Postoperative 2th month	Postoperative 6th month	Postoperative 1st year
KS	15.00	15.00	21.67	23.33	33.33	36.67

Figure 3 Changes observed in the pretest and posttest averages of the patients' Karnofsky performance scale values.

months, when rapid recovery was expected, indicated that natural recovery was unlikely in this patient group.

CONCLUSION

This study underscores the promising potential of MSC transplantation in managing TBI. The efficacy of cell transplantation largely hinges on its impact at the cellular level within the host tissue. Notably, we observed improvements in both motor and cognitive functions, as well as a reduction in spasticity among TBI patients. These transplanted cells play a crucial role in mitigating inflammation within the host tissue and promoting recovery, including the regeneration of damaged nerves. When combined with neurorehabilitation, cellular transplantation significantly contributes to the functional recovery of chronic TBI patients, ultimately enhancing their overall quality of life. The results demonstrate substantial enhancements in motor function within the injured brain tissue. Moving forward, comprehensive comparative studies exploring different cell types and transplantation routes should be conducted meticulously. Rigorous methodological trials, including randomization, blinding strategies, and control groups, are essential for drawing conclusive findings.

FOOTNOTES

Author contributions: Kabatas S and Civelek E contributed to the concept of this study; Kabatas S, Boyalı O, and Savrunlu EC designed the study; Kabatas S, Civelek E, and Karaöz E were involved in the supervision of this article; Kabatas S, Civelek E, Sezen GB, Kaplan N, and Savrunlu EC participated in the analysis and/or interpretation of this manuscript; Kabatas S, Civelek E, Boyalı O, Sezen GB, Ozdemir O, and Bahar-Ozdemir Y contributed to the literature search related to this study; Kabatas S, Civelek E, Sezen GB, Kaplan N, Bahar-Ozdemir Y, Savrunlu EC, and Karaöz E were involved in manuscript writing; Kabatas S, Civelek E, and Ozdemir O contributed to the critical reviews.

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Clinical trial registration statement: Due to local legal restrictions, separate permission was obtained from the Turkish Ministry of Health for each patient included in the study, and therefore clinical trial registration could not be obtained.

Informed consent statement: Written informed consent was obtained from the patients for their anonymized information to be published in this article and before the stem cell therapies.

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