



Research Paper

Safety Evaluation of Umbilical Cord Tissue-derived
Mesenchymal Stem Cells (UC-MSCs) in the Treatment
of Patients With Multiple Sclerosis

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system, leading to symptoms like fatigue, mobility issues, and cognitive decline. Available treatments include disease-modifying therapies (DMTs) and symptom management options. However, many patients experience limited effectiveness, side effects, or inadequate response, highlighting the need for innovative therapeutic approaches. Given the potential of mesenchymal stem cells (MSCs) to modulate immune responses and promote neuroprotection, this study aims to assess safety of umbilical cord-derived MSCs (UC-MSCs), paving the way for future therapeutic applications in MS management.

Materials & Methods: In this study, five patients with MS were selected based on McDonald criteria and specific inclusion criteria, including age, EDSS score, and absence of certain medical conditions. Pre-injection assessments included ECG, MRI, and comprehensive blood and urine tests. Patients received UC-MSCs in normal saline over 20 minutes, followed by hydrocortisone. Post-injection, patients were monitored in the hospital for 24-48 hours, with vital signs checked every 1 to 3 hours. Blood and urine tests were repeated 24 hours after injection and again one month later to evaluate safety and monitor for adverse effects.

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Results: Our result showed that the differences in means for all inflammation and infection, liver function, kidney function, and blood tests over the four time points were not statistically significant.

Conclusion: Given the absence of significant side effects associated with the utilization of UC-MSCs, it can be confidently concluded that these cells represent a promising therapeutic option for the effective management of MS. Their safety profile enhances their potential as a viable treatment alternative for patients.

1. Introduction

Multiple sclerosis (MS) is a chronic, relapsing condition characterized by the formation of plaques in the brain and spinal cord. In MS, the body's immune system targets the myelin sheath surrounding nerve cells in the central nervous system. This attack results in dysfunction of the nervous system, which presents with a range of clinical symptoms [1]. In many patients, the clinical presentation of MS is characterized by reversible neurological symptoms, known as relapsing-remitting MS. Following this phase, individuals may transition into a secondary progressive stage, where they experience lasting neurological deficits and a gradual increase in disability, referred to as secondary progressive MS [2]. The mechanism underlying this disease is autoimmune in nature, with T cells playing a crucial role. Additionally, macrophages and microglia are found in the demyelinated plaques, contributing to the inflammatory processes associated with the condition [3]. Most current treatments focus on managing acute attacks and alleviating symptoms by modulating the immune system. Standard therapies can lower relapse rates, slow down or prevent the progression of disability, and, in some cases, even reduce existing disability [4]. Mesenchymal stem cells (MSCs), which originate from the mesoderm, have the remarkable ability to self-renew. These cells can differentiate into various lineages, allowing them to develop into mesodermal, ectodermal, and endodermal tissues. This versatility makes them a valuable resource in regenerative medicine and tissue engineering [5]. The therapeutic effects of MSCs are closely linked to their ability to differentiate and their paracrine effects. These cells secrete a variety of substances, including cytokines and microRNAs, which play significant roles in mediating their beneficial effects in tissue repair and regeneration [6]. MSCs are immune system modulators and, in addition to their anti-inflammatory properties, they also play a role in stopping apoptosis [7, 8]. Due to the unique properties of MSCs, numerous studies have been conducted across various countries and years. Some of these studies utilized MSCs sourced from the patient's bone

marrow or adipose tissue, while others employed fetal umbilical cord-derived MSCs (UC-MSCs) for treatment. The research has explored different doses and frequencies of injections to assess their efficacy and safety in therapeutic applications [9-12]. In various studies, injections of MSCs were administered via different routes, including intrathecal (IT) and intravascular (IV) methods. Some studies even combined both IV and IT injections. Notably, no serious adverse events or deaths were reported in any of the reviewed studies prior to the project's initiation. However, several adverse events were recorded, such as headaches, infections, cardiovascular complications, and injection site issues [13-19]. Based on the information, the aim of the present study is to evaluate the safety of the purchased UC-MSCs in this research for conducting the subsequent phases of the clinical trial. This assessment is conducted to ensure the safety and usability of these cells in the treatment of patients with multiple sclerosis.

2. Materials and Methods

2.1. Patient selection

Five patients with MS diagnosed according to the McDonald criteria were included in the study based on the inclusion criteria. The inclusion criteria included: age between 18 and 55 years, EDSS score between 2 and 7, patients with secondary progressive MS, absence of hepatitis B and C and HIV diseases and any active infection (White blood cell count (WBC) above 11,000), no history of tuberculosis, no kidney problems (creatinine above 2.5) and cardiovascular and mental problems, no poorly controlled diabetes (HbA1c above 8.5), no history of organ transplantation and no pregnancy in women. Patients were given explanations regarding ethical issues and were told that participation in this study was voluntary and that they could withdraw from the study at any time, and that they would not be deprived of their usual treatments.

Table 1. Mean and standard deviation of hematological and biochemical parameter before and post-infusion

Parameters	Mean±SD				P
	Before Intervention	1 Day after Intervention	A Few Days after Intervention	1 Month after Intervention	
White blood cell count ($\times 10^3/\mu\text{L}$)	7.42±1.76	7.92±2.43	7.06±1.37	8.62±3.77	0.51
Erythrocyte sedimentation rate (mm/hour)	11.4±7.7	6.2±3.11	18.80±21.14	12.4±18.2	0.50
C-reactive protein (mg/L)	4.16±5.51	8.5±15	25.2±31.57	8.02±14.53	0.52
Aspartate aminotransferase (U/L)	20.8±3.56	17.4±3.64	29.5±15.86	24.2±8.01	0.36
Alanine aminotransferase (U/L)	19.4±6.84	17±3.53	30±19.51	21.6±3.84	0.37
Blood urea nitrogen (mg/dL)	13.36±3.52	13.66±2.29	12.5±1.87	15±5.83	0.39
Creatinine (mg/dL)	0.86±0.11	1±0.12	0.89±0.07	0.97±0.02	0.12
Hemoglobin (g/dL)	14.66±1.93	13.74±1.42	14.7±1.95	15.44±1.65	0.25
Platelet count ($\times 10^3/\mu\text{L}$)	302±103.68	278±61.81	246.6±20.37	290.6±71.55	0.23

2.2. Pre-injection checks

A complete history was taken from all patients, and the following tests were performed on them. Before the injection, all patients underwent electrocardiogram and magnetic resonance imaging (MRI). Blood and urine biochemical tests, including CBC, creatinine, BUN, blood sugar, bilirubin, liver enzyme levels including aspartate aminotransferase (AST) and Aspartate aminotransferase (ALT), urine U/A tests, and inflammatory tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were performed.

2.3. UC. MSCs injections

UC-MSCs were procured from Cell Tech Pharmed Company (Iran) and transported to the Neurology Department of Baqiyatallah Hospital in 5 mL vials, each containing 60 million cells, at a temperature below 8 degrees. The contents of each vial diluted in 100 mL of normal saline over a period of 20 minutes. Following each injection, 100 mg of hydrocortisone was administered slowly to each patient.

2.4. Post-injection follow-up

All patients were hospitalized for 24 to 48 hours post-injection, with vital signs monitored every 1 to 3 hours. Twenty-four hours after the injection, and prior to discharge, blood and urine biochemical tests were repeated, including CBC, creatinine, BUN, blood sugar, bilirubin, liver enzyme levels (AST and ALT), urine analysis (U/A), and inflammatory markers (ESR and CRP). All tests were repeated one month post-injection.

2.5. Statistical analysis

Data are expressed as Mean±SD. Changes in before and after mesenchymal stem cell injection were compared over time using a repeated-measures analysis of variance (ANOVA). A $P < 0.05$ was considered statistically significant. All data were analyzed with SPSS software, version 16.0.

3. Results

The Mean±SD of the hematological and biochemical parameters measured at four time points as well as the trends of their changes, are illustrated in Table 1 and Figure 1. The analysis showed that the differences in means for all markers, including those for inflammation, infection, liver function, and kidney function, across the four time points were not statistically significant ($P > 0.05$).

4. Discussion

Numerous studies have been conducted across various regions to assess the safety of MSCs therapy in patients with MS. These studies demonstrate considerable variability in several factors such as including the MSCs source, cell dosage, injections frequency, and method of administration (intravenous, intrathecal, or both). Furthermore, differences in concomitant medications, safety protocols, and follow-up durations across studies likely contribute to the discrepancies observed in reported complications. For instance, Riordan et al. (2018) conducted a study involving 20 patients, each receiving seven doses of UC-MSCs, with each dose consisting of

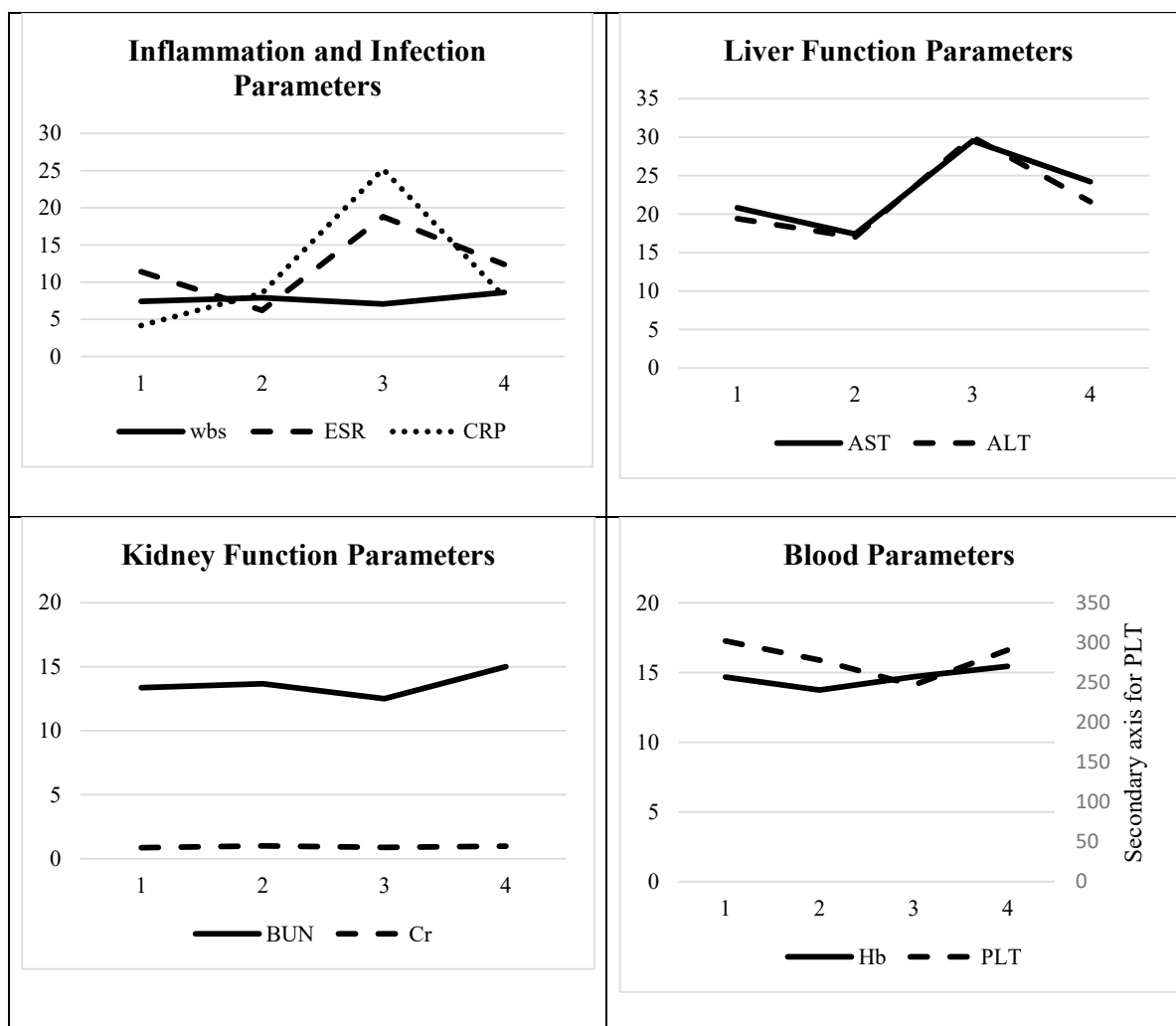


Figure 1. Trends in hematological and biochemical parameters over time

20×10^6 cells, totaling 140×10^6 cells. Over a one-year follow-up period, no serious adverse events were reported. Observed side effects observed were mild to moderate, comprising 66 mild and 6 moderate cases, primarily headaches, fatigue, and cardiovascular and gastrointestinal issues. Importantly, none of these side effects persisted beyond one year, nor did they necessitate study discontinuation [17]. In a 2020 study, Lu et al. examined the safety of infusions of UC-MSCs in patients with progressive relapsing MS. Five patients received low-dose MSCs via four intravenous infusions and three intrathecal injections. The treatment protocol included an initial dose of 40×10^6 cells on the first day, followed by 20×10^6 cells intravenously combined with 20×10^6 cells intrathecally every seven days. Over a 10-year follow-up, no serious complications, such as organ dysfunction or tumor formation, were reported, leading the researchers to conclude that intravenous and intrathecal infusions of UC-MSCs appear to be safe and feasible [18]. Jamali et

al. (2024) evaluate the safety and efficacy of UC-MSCs injections in 35 patients with MS. Patients were divided into two groups: the first group received two doses of UC-MSCs, while the second group received one dose. Additionally, both groups were administered supernatant fluid derived from MSCs three months after the initial injection. The results indicated that all patients tolerated the MSCs injections well, with no severe side effects reported during the one-year follow-up, reported mild side effects, such as headaches and mild fever, resolved within the first month [19].

In this study involving 5 patients, the one-month follow-up revealed that 3 patients reported no complaints at all. One patient was hospitalized twice: once due to fever and chills, and another time for a lung infection, but he recovered following treatment. Additionally, another patient was monitored in the hospital for several days due to abnormal post-injection laboratory, but was

discharged after clinical improvement, reporting no new issues related to their existing condition during the one-month follow-up. Among the 5 patients in the study, 2 of them experienced changes in their laboratory results, specifically in inflammatory tests such as ESR, CRP, and WBC count. One of these two patients showed no findings on examination or culture results indicating infection and was discharged in good general condition after necessary evaluations. Within a month, their laboratory results returned to nearly normal levels. The second patient, who was hospitalized initially with fever, chills, and laboratory changes following the injection, recovered within 24 hours. However, this patient was treated again about two weeks later for pneumonia. It remained unclear whether this infection was related to the injection or was merely coincidental. Similar to the previous study, fever was noted as a complication in one patient. Additionally, changes in inflammatory tests were observed in two patients, which could potentially be linked to the injection or a mild non-severe infection. Overall, no severe complications were reported among the 5 patients during the one-month follow-up, suggesting that injecting UC-MSCs may be feasible and safe for MS patients in the short term. However more comprehensive studies with larger cohorts and extended follow-up periods are necessary to draw definitive conclusions. The limitations of this study include a small sample size, which may affect the generalizability of the results, and an insufficient follow-up duration to assess long-term safety and efficacy. Additionally, the lack of an appropriate control group may introduce bias when evaluating treatment effects. Variability in treatment protocols and safety assessment methods could also result in inconsistent outcomes, and the specific patient selection may limit the broader applicability of the findings.

5. Conclusion

In summary, we investigated the feasibility and safety of administering 60 million UC-MSCs to patients with MS who were also undergoing treatment with monoclonal antibodies. Our results indicate that this method could be a promising strategy for improving treatment outcomes in MS patients. Nonetheless, additional research with larger sample sizes and extended follow-up is essential to comprehensively evaluate the long-term safety and effectiveness of UC-MSCs in this setting.

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Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of [Baqiyatallah University of Medical Sciences](#), Tehran, Iran (Code: IR.BMSU.BAQ.REC.1402.031) and was also registered by the Iranian Registry of Clinical Trials (IRCT), Tehran, Iran (Code: IRCT20230806059052N1).

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Authors' contributions

Conceptualization: Seyed Javad Hosseini Nejad Anbaran; Data curation, investigation, and writing the original draft: Mohamad Mahdi Esmacili Araghi and Hadi Esmacili Gouvarchin Ghaleh; Formal analysis: Mehdi Raei and Akbar Ghorbani Alvanegh; Methodology, validation and software: Mehdi Raei, Akbar Ghorbani Alvanegh, and Bahman Jalali Kondori; Review and editing: Mohamad Mahdi Esmacili Araghi, Mehrdad Moosazadeh Moghaddam, Hadi Esmacili Gouvarchin Ghaleh, Mehdi Raei, Bahman Jalali Kondori, Akbar Ghorbani Alvanegh and Seyed Javad Hosseini Nejad Anbaran.

Conflict of interest

The authors declared no conflict of interest.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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