

Safety and Efficacy of Bone Marrow and Adipose Tissue Mesenchymal Stem Cells in the Treatment of Spinal Cord Injury: A Preliminary Study

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Abstract

Background: Mesenchymal stem cells (MSCs) of various origins are the most widely investigated type of stem cells in clinical trials. We report a treatment comparison of two adult sources of autologous MSCs regarding safety and efficacy in established spinal cord injury (SCI).

Materials and Methods: In this Phase I/II open-label two-arm study, patients were divided into two groups. The first group was treated with autologous bone marrow-derived MSCs (BM-MSCs), while the second was treated with autologous adipose tissue-derived MSCs (AT-MSCs). Safety and outcomes were assessed in both groups for 24 months post-treatment initiation using the American Spinal Injury Association (ASIA) Impairment Scale (AIS).

Results: Both groups showed no serious treatment-emergent adverse events (TEAEs). AIS-assessed outcomes pointed to sensory and motor improvements in patients of both groups. Patients who received AT-MSCs showed better sensory and motor function improvement than those who received BM-MSCs. One patient in the AT-MSCs group regained the ability to walk after years of disability.

Conclusions: Intrathecal injection of autologous AT-MSCs and autologous BM-MSC appears to be safe, with a possible advantage in the AT-MSCs treatment option regarding efficacy over BM-MSCs. Future clinical trials investigating larger sample sizes are warranted for wider use of this treatment modality in clinical practice. Furthermore, earlier use of cellular therapy intervention for SCI patients is predicted to improve the benefits.

Trial registration: clinicaltrials.gov identifier: NCT02981576

Keywords: Adipose tissue-derived mesenchymal stem cells; American Spinal Injury Association Impairment Scale; bone marrow-derived mesenchymal stem cells, cell therapy; central nervous system, light touch assessment; motor function, pinprick sensation paralysis; regenerative medicine; sensory dysfunction; spinal cord injury

Abbreviations:

TEAE: Treatment-emergent adverse event

ASIA: American Spinal Injury Association

AT: Adipose tissue

BM: Bone marrow

CTC: Cell Therapy Center

MSCs: Mesenchymal stem cells

SCI: Spinal cord injury

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INTRODUCTION

Spinal cord injury (SCI) is a crippling central nervous system condition that can lead to voluntary motor, sensory and autonomic nervous system dysfunction [1]. This serious condition affects patients' mental health and social interactions [2]. Neurological dysfunction is caused mainly by two mechanisms: primary damage is due to direct trauma to the spinal cord, and secondary damage is caused by disrupted blood flow, tissue oedema and inflammation, oxygen-free radicals, and scar formation within neural tissue [3].

The current management of SCI cases has limited efficacy. It usually consists of an immobilization of the spine with decompression to reduce the extent of the traumatic injury in addition to steroids [2, 4]. Other treatment modalities, such as surgical intervention or physiological rehabilitation for chronic SCI, do not produce satisfactory outcomes [2, 5, 6].

Regenerative medicine using cellular therapy is an emerging treatment field with promising outcomes attributed to the cells' ability to differentiate into neuronal cells, remyelination of the neurons, and alteration of the interstitial environment to one favoring the neural repair process [7]. These regenerative abilities have been reported in clinical and preclinical studies and attributed to mesenchymal stem cells (MSCs). Nevertheless, a consensus on the MSC protocol leading to the best results has not yet been reached. The lack of standardization for stem cell preparation and administration has made it difficult to evaluate the various trials treating SCI.

Mesenchymal stem cell treatment is a promising modality for reducing the impact of secondary injury. It has the potential to reduce inflammation, induce differentiation into various neural tissue cells, and aid nerve tissue regeneration [2, 6, 8–10]. The use of MSCs in SCI treatment is considered a good alternative to embryonic stem cells, as there is a lack of consensus regarding the latter due to ethical considerations associated with their harvest and use in therapy [11]. MSCs derived from bone marrow (BM-MSCs) were the first to be used in clinical trials, followed by MSCs derived from adipose tissue (AT-MSCs). This is due to their accessibility

for use as adult autologous cells. Studies treating SCI patients with autologous BM-MSCs or autologous AT-MSCs have shown promising results with satisfactory safety outcomes. However, trials differ in many aspects, such as the number of cells administered, the stem cell isolation procedure, the cell-culture preparation method, the route of injection, the type of injury, and the post-treatment assessment procedure [12–15]. Moreover, no study has compared these two types of MSC when cultured under the same conditions and administered in similar numbers via the same route.

In this comparative open-label phase I/II work, the primary aim was to study the safety of intrathecal administration of expanded autologous MSCs from bone marrow and adipose tissue, respectively. The secondary endpoint was to evaluate and compare the efficacy of both MSC treatments.

MATERIALS AND METHODS

Study participants and sampling technique

This study was approved by the institutional review board of the Cell Therapy Center (CTC) at the University of Jordan. The patient cohort included 14 patients with complete and incomplete spinal cord injuries. They were examined at the CTC between December 2016 and September 2017 for eligibility and enrollment. However, six patients were lost to follow-up and, therefore, were not included in the analysis. Figure 1 presents a flowchart of the study. Patients were enrolled if they were older than 18 years of age, had an American Spinal Injury Association (ASIA) grade A, B, or C spinal cord injury, and presented to the CTC at least 12 months post-injury. Patients were excluded if they demonstrated any of the following: reduced cognition, significant osteoporosis in the spine and/or joints, pregnancy (adequate contraceptive use is required for women of fertile age), anoxic brain injury, neurodegenerative diseases, evidence of meningitis, positive serology for HIV, HBV, HCV, syphilis, or medical complications that contraindicate intervention. Furthermore, uncorrected vision, cardiac abnormalities, uncontrolled hypertension, diabetes mellitus, and an inability to provide informed consent rendered the patients ineligible in this trial.

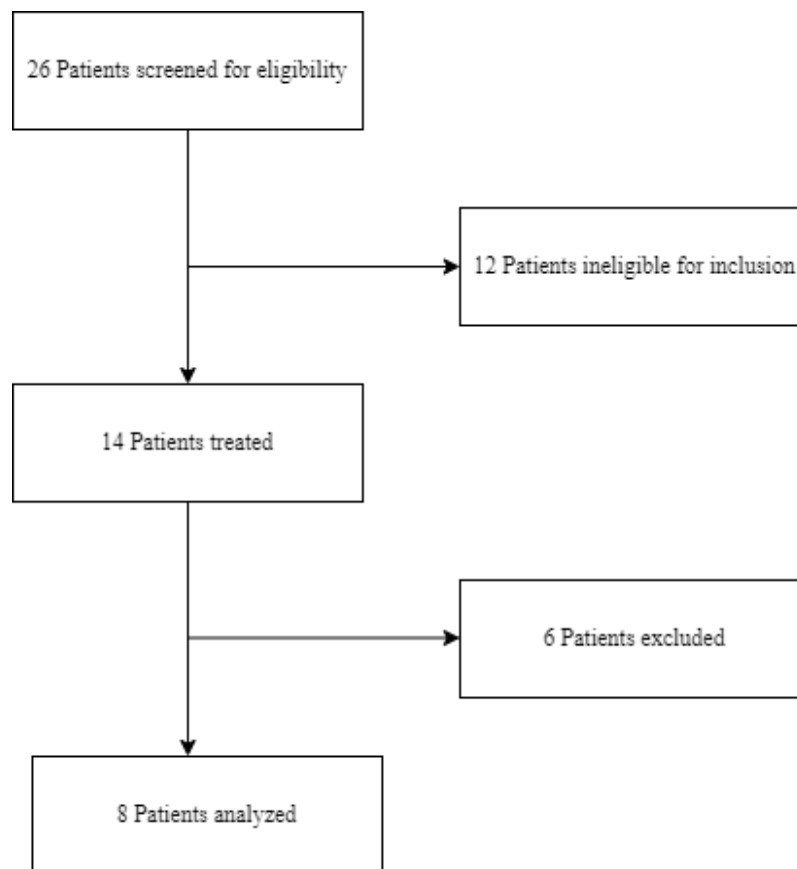


Figure 1: Flowchart of the study

Trained research personnel explained the benefits and risks of treatment during the consent meetings. Informed consent was obtained from participating patients prior to enrollment in accordance with the Helsinki Declaration.

Stem Cell Preparation

BM-MSCs and AT-MSCs were prepared from each patient's bone marrow or adipose tissue according to established protocols and following CTC standard operation procedures (SOP) [9]. Briefly, bone marrow and adipose tissue biopsies were processed immediately and cultured in treated tissue culture flasks. Alpha MEM media supplemented with 5% in-house prepared human platelet lysate was used to obtain xenogeneic-free stem cell expansion media. The release criteria for all MSCs were in accordance with the International Society for Stem Cell Research (ISSCR) and Society for Cellular Therapy (ISCT) minimum MSCs characterization criteria. This included

differentiation potential and surface marker expression in addition to the spindle shape morphology and plastic adherence property of spindle-shaped cells. Differentiation potential assessment of the isolated MSCs was performed using StemProR adipogenesis and osteogenesis differentiation kits (GIBCO, NY, USA) according to the manufacturer's instructions. Cells at passages 3–5 were used in differentiation experiments. To detect adipogenic and osteogenic differentiation, oil red O stain and alizarin red S were used, respectively. Flow cytometry analysis of the MSCs' surface markers, as isolated from both sources, was performed using a Stemflow™ hMSC analysis kit (BD Biosciences, CA, USA) according to the manufacturer's instructions. Cells were stained with antibodies against CD73, CD90, CD105, CD44, CD34, CD11b, CD19, CD45 and HLA-DR. The percentage of expressed cell surface markers was calculated from a minimum of 10,000 gated cells

using BD FACSCanto™ Clinical Software.

MSCs Injection Protocol

After baseline clinical examination, patients in both groups were intrathecally injected with a total of four doses of their respective MSCs by standard lumbar puncture technique at the L3–L4 spinal interspace. Each dose was intended to be 100×10^6 , separated by a 30 ± 3 -day margin.

Safety and Efficacy Evaluation

Eligible patients provided informed consent after they had acquired satisfactory knowledge of treatment, follow-up procedure, and possible side effects. Patients were then randomly allocated to two interventional groups. They were enrolled in the AT-MSCs group or the BM-MSCs group. Patients in both groups underwent a preliminary neurological examination. At 12 months and 24 months post the first dose, patients were neurologically re-evaluated.

Patients were evaluated for treatment efficacy and safety by a specialized examiner who was blinded to the type of MSCs administered. The safety of treatment was assessed by a survey given one hour, 24 hours, six months, and 12 months after each dose, assessing any treatment-emergent adverse event (TEAE).

Neurological parameters such as motor functions and sensory sensations were evaluated according to the ASIA impairment scale [16]. Severity grades range from A to E, with A being the most severe injury impact and E being the least. In grade A, the impairment is complete; there is no motor or sensory function below the level of injury. Examined parameters included motor function, light touch, pinprick sensation, deep anal pressure, and voluntary anal contraction.

Statistical analysis

Data were entered into an Excel spreadsheet and analyzed using SPSS v.23 (Chicago, IL, USA).

Patient data were presented as means $\pm$ standard deviations and frequencies. Significant differences in neurological scores before and after the administration of treatment were measured using a t-test. Data were analyzed under the following assumptions: 5% alpha error and 95% confidence interval. Associations with a *p*-value of less than 0.05 were considered statistically significant.

RESULTS

An analysis of the stem cell treatment safety and efficacy of eight SCI patients with varying degrees of spinal cord injury was performed. The participants were equally split between the two treatments (BM-MSCs, *n*=4; AT-MSCs, *n*=4).

For the entire cohort, post-treatment headache was the most reported side effect on day one (50%). Mild involuntary muscle contraction was the most frequent side effect at one week post-treatment (50%). Contractions were the most observed long-term side effect (50%), followed by numbness (12.5%), and pain at the injection site (12.5%). No long-term TEAEs were reported for all treated patients.

The clinical characteristics of patients of both groups are summarized in Table 1. The mean age of the four patients treated with BM-MSCs was 33.00 (± 6.27) years. Three patients of this subgroup had a baseline ASIA grade of A, and one patient had a grade of B. Of the included patients, three improved; one had both motor and sensory improvements, one had sensory improvement, and the third had motor neurological improvements. Among these patients, total ASIA score, light touch, pinprick, and motor function scores were improved throughout the study's follow-up period. Two of the recruited patients had ASIA grade improvements from A to B.

Table 1: Baseline characteristics and overall treatment results of individual participants in each study arm

Participant	Gender	Type of Injury	Injury Level	Injury Period (Before enrollment) "years"	Baseline ASIA Grade (in numbers)	Year 1 ASIA Grade (in numbers)	Year 2 ASIA Grade (in numbers)
BM-MSCs							
P1	M	FA	T4-T8	6	A (138)	A (138)	A (138)
P2	M	RTA	C4-C5	2	A (128)	B (144)	B (154)
P3	M	FA	T2	3	A (190)	A (190)	A (218)
P4	M	RTA	T12	5	B (264)	B (267)	B (267)
AT-MSCs							
P5	M	RTA	L1	2	A (202)	C (258)	D (309)
P6	M	RTA	T11	5	A (170)	B (180)	B (190)
P7	F	FA	T12-L1	5	C (254)	C (258)	C (274)
P8	M	FA	C5-C7	2	A (106)	A (116)	B (124)

P, Patient; ASIA, American Spinal Cord Injury Association; AT, Adipose Tissue; BM, Bone Marrow; MSC, Mesenchymal Stem Cell; M, Male; F, Female; RTA, Road Traffic Accident; FA, Fall

The mean age of the four patients treated with AT-MSCs was 35.25 ± 12.25 years. Grade C ASIA was observed in one patient, while the other three had grade A. All patients in this treatment group had neurological improvements; two had motor and sensory improvements, while the other two had sensory improvements. Improvements in ASIA grade to B, C, and D were observed in three patients in this subgroup, and one patient gained voluntary anal contraction (VAC). The patients' total ASIA score, light touch, motor, and pinprick scores improved throughout the study. One patient had a remarkable motor recovery as he regained his ability to walk and drive a motor vehicle.

DISCUSSION

This study's focus has been on the safety and efficacy outcomes of injecting two types of MSCs, BM-MSC and AT-MSC, into patients with chronic spinal cord injuries. MSCs were expanded under the same culture conditions and administered intrathecally in similar numbers. The expansion of both MSC groups was conducted using the same culture conditions, including human platelet-enriched defibrinated plasma as a xenogeneic-free supplement, thus reducing lab-to-lab variability in cell preparation protocols.

Both MSC treatments were safe in all patients without any reported serious side effects or long-term TEAEs. On the first day of treatment, patients reported mild headaches, while mild muscle contractions were reported a week after treatment. The 24-month follow-up period was longer than most similar safety studies that use 12 months as the

endpoint. Although the long duration of this trial contributed to participant attrition, it confirmed the previously reported overall safety of cellular therapy in the long term [11, 13–15, 17].

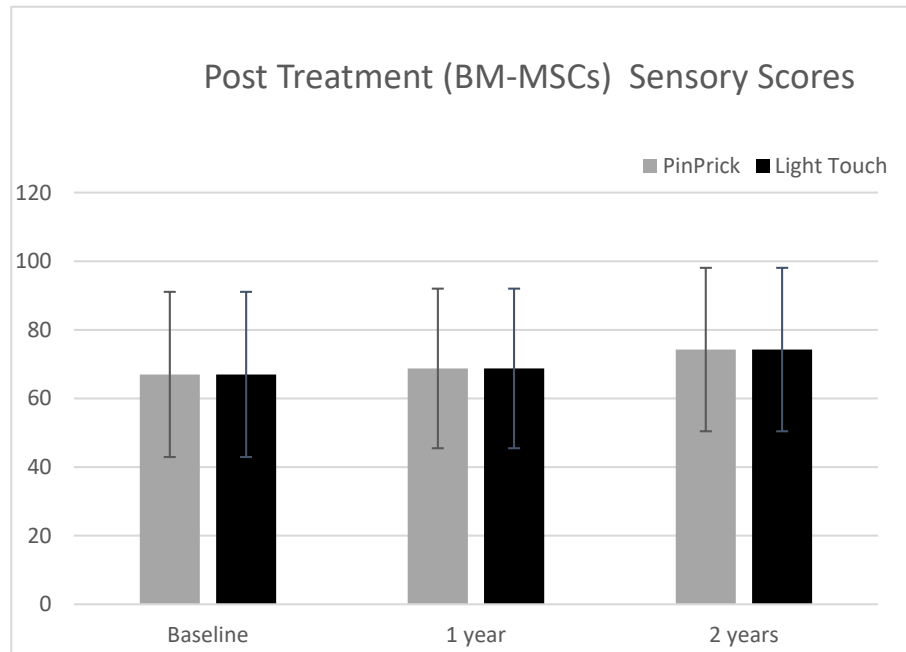
Treatment efficacy varied between the two groups and among patients in the same group. The patients enrolled in the study were injured at least two years prior to treatment. This period accounts for natural neurological improvements observed in some SCI cases, which plateau after a year post-primary injury [17]. Thus, reported changes post-intervention can be more confidently attributed to stem cell therapy. However, low participant numbers prevented statistical significance.

Analyzing therapeutic benefits in the BM-MSC group (four doses of $11.675 \pm 5.511 \times 10^7$ cells) showed improvement in three out of four patients (75%) with an overall improvement in the ASIA score in two out of the four patients, who moved from an ASIA grade A to B (P2, P4). There was an improvement in light touch and pinprick sensation of 13 and 14 points, respectively, in two out of four patients (P2 & P3) (Figure 2). Motor function improvements of 2 and 3 levels were observed in two patients, P2 and P4, respectively. However, P2 lost motor improvements at the two-year mark. Our findings are comparable to previously reported studies using BM-MSCs as a treatment modality for SCI, although each followed a different protocol. Vaquero et al. [18] administered a single dose of autologous BM-MSCs (1.8×10^8 cells) in ten patients via the intrathecal route. They reported a 60% motor function improvement with improved sensory function in all patients. Moreover, El-Kheir

et al. [14] obtained similar results in their study, in which autologous BM-MSCs (2.0×10^6 cells/kg) and physiotherapy were used to treat 50 SCI patients; they observed a 52% improvement in motor function and a 46% improvement in all parameters. In a large

study enrolling 264 patients and using a similar number of cells per dose (10×10^7 cells), Kumar et al. [13] showed a lower motor and sensory function improvement of ~32%.

A)



B)

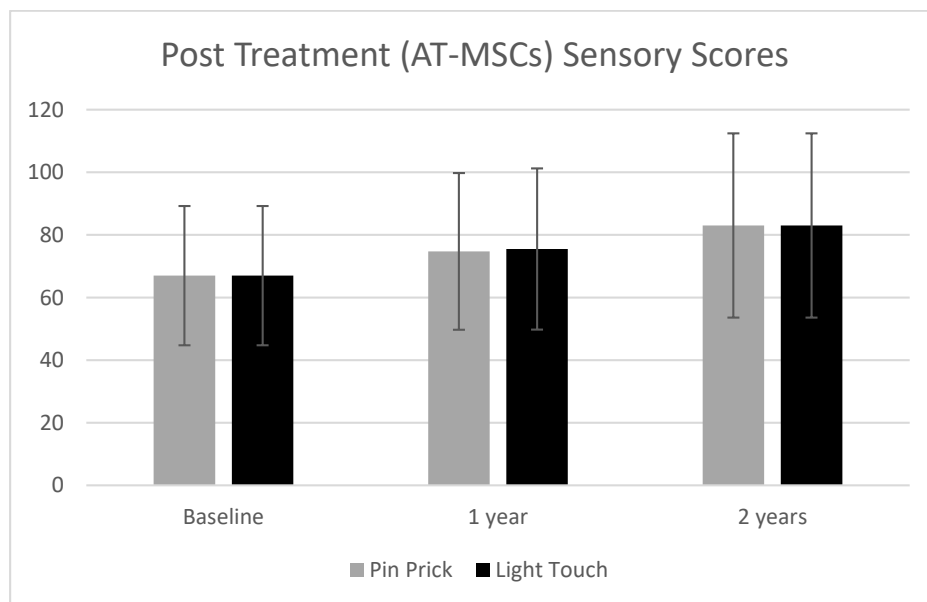


Figure 2: Means of changes in sensory scores according to ASIA of patients in both sub-groups, those receiving BM-MSC (A) and those receiving AT-MSCs (B)

ASIA, American Spinal Cord Injury Association; BM, bone marrow; MSC, mesenchymal stem cell

On the other hand, all patients receiving AT-MSCs ($9.213 \pm 4.01 \times 10^7$ cells) improved in terms of light touch and pinprick sensations at a magnitude of 16 (± 13.7) points (Figure 2). Two of the four patients experienced an improvement in motor function of 35 and 2 points in (P5 and P8, respectively), which reflected an overall improvement trend in this group (Figure 3). Two patients moved from ASIA grade A to B (P6 and P7), whereas a third patient (P8) showed a remarkable improvement from ASIA grade A to D. The same patient developed voluntary anal contraction (VAC) and started walking progressively after years of being bound to a wheelchair. At one year post-stem cell treatment, P8 was able to walk a few steps and was capable of driving his automobile by the end of the

second year. It is noteworthy that this patient was highly enthusiastic and followed an exercise program on his own, which was not part of the protocol but was not contraindicated either. The use of AT-MSCs to treat SCI was reported in two clinical trials, both of which had lower efficacy. The first clinical trial used the intravenous (IV) route to inject eight patients with a high dose of AT-MSCs 40×10^7 cells), in which motor function improvement was reported in three patients and a gain of sensory function in one patient [15]. The second study analyzed eight patients who received an intrathecal injection of 9×10^7 AT-MSCs and reported motor and sensory function improvement in two and five patients, respectively [11].

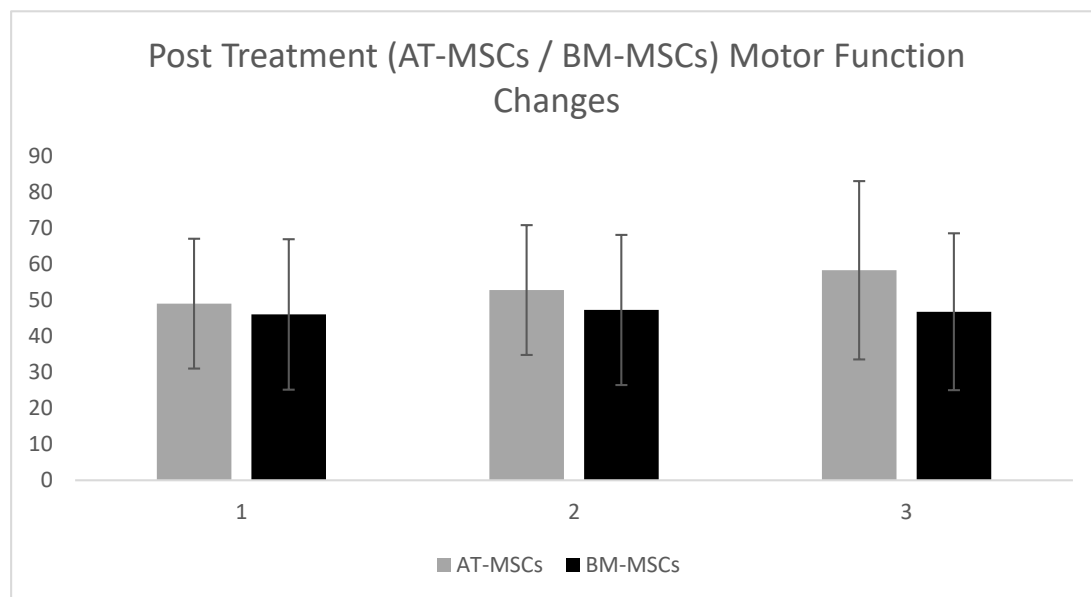


Figure 3: Means of the motor component of the ASIA scores for patients by sub-group; those receiving BM-MSC or AT-MSCs at baseline (1), one year (2) and two years (2)
 ASIA, American Spinal Cord Injury Association; AT, adipose tissue; BM, bone marrow; MSC, mesenchymal stem cell

The benefits reported in both treatment groups can be linked to the molecular characteristics of BM-MSCs and AT-MSCs. In silico work by our group pointed to the immune modulating potential necessary for SCI healing in both MSC types, with more GO-TERMS in BM-MSCs. This was attributed to BM-MSCs through a higher expression of immune-regulating genes, including CD200 and IL-17, and to AT-MSCs through the expression of the novel and potent immune-regulator CD276 [9].

Although the BM-MSC subtype has dominated human clinical trials of MSCs, it is noticeable that

AT-MSCs have now gained momentum over BM-MSCs. This is mostly due to the rate of retrieved stem cells from adipose tissue at $\geq 0.01\%$, compared to only $\sim 0.001\%$ from bone marrow aspirates [19]. Furthermore, a previous pre-clinical study pointed to the higher therapeutic potential of AT-MSCs over BM-MSCs in the treatment of spinal cord injury [10]. The use of AT-MSCs may have an additional inherent advantage over BM-MSCs in terms of their lower expression of HLA-DR Class II MHC and HLA-C Class I MHC and, thus, a decreased immunogenicity [9]. This could be of value for

future studies in which an allogeneic source would be administered to eliminate discrepancies in number and secretome profile linked to autologous MSCs treatment.

Since this and previously published studies have demonstrated the safety of intrathecal MSCs injection [13–15], an earlier use of cellular therapy intervention for SCI patients is recommended in order to maximize the benefit by limiting inflammation and promoting regeneration at the site of injury. A combination of cellular and physiotherapy programs can also enhance the benefits of this treatment modality [7].

Overall, the 24-month follow-up period of this study, which is longer than most reported stem cell safety studies, contributed positively to considering both BM-MSCs and AT-MSC treatments as safe options for SCI cases. Although efficacy was concluded from a small number of SCI patients, thus lacking statistical power, our results suggest the substantial benefit of AT-MSCs treatment over BM-MSCs. Nevertheless, a larger clinical trial with a control group (receiving a placebo) might be needed for a statistically significant inference.

CONCLUSION

In this study, the intrathecal injection of autologous stem cells into SCI patients was found to be safe. The

use of AT-MSCs showed better sensory and motor function outcomes than BM-MSCs. No serious adverse events in either group were recorded. This reiterates the fact that MSC therapy holds the potential to enhance neurological function in patients with chronic SCI, and its administration in the early stages of the injury needs to be investigated. Further investigations into both sub-groups with larger sample sizes are warranted for such treatments to be implemented in conventional practice.

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Competing Interests: All contributing authors have no conflict of interest related to this study.

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دراسة سلامة وفعالية الخلايا الجذعية الوسيطة المستخلصة من نخاع العظمي والأنسجة الدهنية في علاج إصابة الحبل الشوكي: دراسة أولية

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الملخص

الخلفية: الخلايا الجذعية الوسيطة (Mesenchymal Stem Cells) المستخلصة من أنسجة مختلفة هي أكثر أنواع الخلايا الجذعية التي تم بحثها على نطاق واسع في الدراسات السريرية. تهدف هذه الدراسة إلى مقارنة علاج مرضى إصابة الحبل الشوكي باستخدام مصدرين بالغين من الخلايا الجذعية الذاتية من حيث السلامة والفعالية.

المواد والطرق: في هذه الدراسة السريرية (المرحلة الأولى / الثانية)، تم تقسيم المرضى إلى مجموعتين. عولجت المجموعة الأولى باستخدام خلايا مشتقة من نخاع العظام، بينما عولجت المجموعة الثانية باستخدام خلايا مشتقة من الأنسجة الدهنية. تم تقييم السلامة والنتائج في كلا المجموعتين لمدة 24 شهراً بعد بدء العلاج وذلك باستخدام مقياس الضرر لجمعية إصابات العمود الفقري الأمريكية.

النتائج: لم تظهر كلا المجموعتين أي أعراض سلبية طارئة خطيرة. كما أشارت النتائج إلى تحسن في الوظائف الحسية والحركية للمرضى من كلا المجموعتين. أظهر المرضى الذين تلقوا خلايا جذعية مشتقة من الأنسجة الدهنية تحسناً أفضل في الوظائف الحسية والحركية من أولئك الذين تلقوا خلايا جذعية مشتقة من نخاع العظام. حيث بلغ التحسن إلى استعادة مريض واحد في تلك المجموعة القدرة على المشي بعد سنوات من الإعاقة.

الاستنتاجات: تظهر الدراسة أن حقن الخلايا الجذعية الذاتية من كلا النسيجين آمن مع ميزة محتملة للنسيج الدهني من حيث الفعالية. تدعم هذه النتائج إجراء دراسات سريرية مستقبلية تعالج عدد أكبر من المصابين. علاوة على ذلك، من المتوقع أن يؤدي الاستخدام المبكر للعلاج الخلوي لمرضى إصابات النخاع الشوكي إلى فوائد أكبر.

تسجيل الدراسة السريرية: Clinicaltrials.gov معرف: NCT02981576

الكلمات الدالة: الخلايا الجذعية الوسيطة المشتقة من الأنسجة الدهنية؛ مقياس ضعف الجمعية الأمريكية لإصابات العمود الفقري؛ الخلايا الجذعية المشتقة من نخاع العظمي؛ العلاج بالخلايا، الجهاز العصبي المركزي؛ تقييم اللمس الخفيف؛ تقييم الوظائف الحركية؛ الإحساس بوخز الدبوس؛ الشلل؛ الطب التجديدي؛ الخلل الحسي؛ إصابة الحبل الشوكي.