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Image-guided percutaneous intralesional administration of mesenchymal stromal cells in subjects with chronic complete spinal cord injury: a pilot study

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Abstract

Background aims. The potential of cell therapies to improve neurological function in subjects with spinal cord injury (SCI) is currently under investigation. In this context, the choice of cell type, dose, route and administration regimen are key factors. Mesenchymal stromal cells (MSCs) can be easily obtained, expanded and are suitable for autologous transplantation. Here we conducted a pilot study that evaluated safety, feasibility and potential efficacy of intralesional MSCs transplantation performed through image-guided percutaneous injection, in subjects with chronic complete SCI. *Methods.* Five subjects with chronic traumatic SCI (>6 months), at thoracic level, classified as American Spinal Cord Injury Association impairment scale (AIS) grade A, complete injury, were included. Somatosensory evoked potentials (SSEP), spinal magnetic resonance imaging (MRI) and urodynamics were assessed before and after treatment. Autologous MSCs were injected directly into the lesion site through percutaneous injection guided by computerized tomography (CT). *Results.* Tomography-guided percutaneous cell transplantation was a safe procedure without adverse effects. All subjects displayed improvements in spinal cord independence measure (SCIM) scores and functional independence measure (FIM), mainly due to improvements in bowel movements and regularity. Three subjects showed improved sensitivity to tactile stimulation. Two subjects improved AIS grade to B, incomplete injury, although this was sustained in only one of them during the study follow-up. *Conclusion.* Autologous bone marrow MSC transplantation, performed through CT-guided percutaneous injection, was shown to be safe and feasible. Further studies are required to demonstrate efficacy of this therapeutic scheme.

Key Words: *cell therapy, clinical study, mesenchymal stromal cells, spinal cord injury*

Introduction

Traumatic spinal cord injury (SCI) often leads to irreversible disability in working-age subjects due to paralysis. Treatment options currently available are limited and mainly directed to the acute phase (i.e., high-dose steroids and surgical interventions) [1]. For subjects with chronic paraplegia, medical care focuses on preventing complications, relieving pain and maximizing residual function through the rehabilitation process [2].

In the last few years, many efforts have been directed toward the translation of stem cells "from bench to the bedside" as a promising approach to promote neurological and functional recovery in subjects with chronic SCI. Different cell types have been tested in the pre-clinical setting, including mesenchymal stromal cells (MSC), neural progenitor cells, olfactory ensheathing cells and oligodendrocyte precursors, with promising results [3–7]. More recently, early-stage clinical trials were performed, evaluating safety and potential efficacy of therapies

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with different cell types, with modest results reported [8–11].

MSCs offer advantages over other cell types that are currently under clinical investigation, being easily obtainable and expandable, with less controversial ethical concerns [12]. Moreover, MSCs can be used in autologous or allogeneic treatments because minimal immunoreactivity has been reported so far [13]. MSCs are multipotent, being able to classically differentiate into mesodermal lineages, while non-mesodermal lineage differentiation has also been reported, including the ability to differentiate into neuron and glial-like cells [14,15]. However, MSCs are able to promote trophic and regenerative support to injured tissues mainly through the secretion of soluble factors, release of extracellular vesicles containing messenger RNA (mRNA) and microRNAs, mitochondrial transfer, among others [16]. Through bystander effects, MSCs were shown to promote axonal growth, myelination and neuronal survival in experimentally induced SCI [17–19].

In previous studies, our group described neurological improvements associated with autologous bone marrow–derived MSCs transplanted directly into the lesion site of dogs and cats with naturally acquired SCI [20,21]. We then conducted a phase 1/2 clinical trial to evaluate the safety and potential benefits of autologous bone marrow MSC transplantation, performed through open surgery with laminectomy in subjects with complete chronic thoracic and lumbar traumatic SCI [11]. This cell delivery method is of high complexity, requires longer periods of hospitalization and precludes the possibility of performing repeated cell administrations, which may be required in cellular therapy protocols. Aiming at reducing complexity and invasiveness of cell delivery, we conducted a prospective pilot clinical study in which a modified strategy for intralesional cell transplantation was evaluated, consisting of a percutaneous, image-guided injection, eliminating the need for open surgery.

Methods

Ethics statement

This study was approved by the Ethics Committee of São Rafael Hospital and was registered on the National Institutes of Health (NIH) database (http://www.clinicaltrials.gov) under the number NCT02152657. Ethical guideline provisions from the Helsinki Declaration were followed. A written consent for participation and for publication was obtained from the subjects.

Objectives and outcomes

The main objective was to evaluate the safety and feasibility of autologous bone marrow–derived MSC transplantation through percutaneous injection in subjects with chronic traumatic SCI. The safety outcome was measured by screening for deleterious modifications on magnetic resonance imaging (MRI), as well as possible side effects and adverse events related to the protocol procedures. The secondary objective was to assess potential efficacy, through neurological improvements in sensory and motor assessment (measured using American Spinal Injury Association [ASIA] scores), pain scores, urodynamics and evoked potential studies. Functional improvements were measured using spinal cord independence measure (SCIM) scores and functional independence measure (FIM). All data were collected personally by the same researchers, with specific forms and validated questionnaires, to enhance the quality of measurements and results.

Subjects selection

From 21 volunteers screened for eligibility, 8 were considered eligible and 5 were included following the order of first contact date. The inclusion criteria were as follows: traumatic SCI at the thoracic level less than T8 for at least 1 year, ASIA impairment scale (AIS) grade A and age ≥18 and ≤65 years. The exclusion criteria were as follows: open SCI, concurrent infectious disease, terminal illness, neurodegenerative disorders, primary hematologic disorders, osteopathies, coagulopathies, hepatic dysfunction, other clinical complications that could contraindicate the procedure, use of metallic implants that contraindicate MRI and participation in other clinical trials.

Participants and researchers, those administering the interventions and those assessing the outcomes were not blinded to the study condition. All data were collected at Hospital São Rafael in Salvador, Bahia, Brazil.

Isolation of bone marrow cells and MSC culture

Prior to bone marrow harvest, subjects were evaluated for hematology, blood biochemistry and urine microbiology and screened for infectious diseases (human immunodeficiency virus [HIV], human T-lymphotropic virus [HTLV], Chagas disease and hepatitis B and C). Bone marrow aspiration was performed by a hematologist in an outpatient surgery center. Subjects were sedated and monitored by an anesthesiologist. Local anesthesia with 2% lidocaine was performed and approximately 60 mL of bone marrow were collected from the anterior and posterior iliac crest using a bone marrow aspiration needle with adjustable length (1.0–4.8 cm) and 15 gauge (Carefusion), and 20-mL syringes containing 1 mL of heparin 5000 IU (Cristália).

The syringes containing bone marrow cells were sent to a certified Current Good Manufacturing Practice (cGMP) facility, at São Rafael Hospital, for

processing under standard protocols, as previously described [11]. MSCs were expanded for approximately 4 weeks. Confluent autologous MSCs at passage three or four resuspended in 5% dextrose in water solution (278 mmol/L; B Braun) in a concentration of 2×10^7 cells/mL were transferred into 1-mL syringes for administration to subjects. Prior to injection, the cells were characterized by immunophenotying in flow cytometry analysis, differentiation assays and G-band karyotype analysis and were tested for sterility and endotoxin.

Differentiation assays

The multipotency of MSCs was confirmed by adipogenic and osteogenic differentiation assays using commercially available kits following the manufacturer's recommendations (StemPro adipogenesis, and Osteogenesis Differentiation Kits; GIBCO). Histochemical staining was used to evaluate cell morphology in differentiated cultures: oil red for visualization of lipid inclusions (adipocytes) and alizarin red for visualization of mineralized matrix (osteoblasts). Images were captured using an AX70 optical microscope (Olympus).

Flow cytometry analysis

MSCs were dissociated with 0.25% trypsin solution (ThermoFisher Scientific), washed with phosphate-buffered saline (PBS) and incubated for 30 min at 4°C with the following antibodies: fluorescein isothiocyanate (FITC) anti-CD11b, PerCP anti-CD45 (Beckman Coulter), peridinin chlorophyll protein complex (PerCP) anti-CD73, Phycoerythrin-Cy5 (PE-Cy5) anti-CD117, allophycocyanin (APC) anti-CD90, APC anti-CD44 (BD-Pharmingen) and FITC anti-CD105 (R&D Systems). Acquisition and analysis were done using a LSR Fortessa cytometer with the FACSDiva software (Becton Dickinson). At least 10 000 events were collected.

Cytogenetic evaluation

G-band karyotype analyses were performed prior to transplantation to detect possible structural and numerical alterations in chromosomes induced by *in vitro* expansion. MSCs were treated with 16 µg/mL colchicine (Cultilab) for a period of 6 h. Then, cells were trypsinized, resuspended, centrifuged, exposed to hypotonic solution of 0.075 mol/L KCl, placed in a water bath at 37°C for 30 min and fixed with Carnoy's solution 3:1 (acetic acid/methanol).

Cytogenetic analysis was performed by Giemsa-banding karyotype. Slides were incubated at 60°C overnight and subjected to treatment with a solution of 0.1% trypsin and subsequently stained with Giemsa solution. Analyses were performed in 20 cells for each passage, by observation in a BX61 microscope (Olympus) and images were captured using a digital imaging system (Applied Spectral Imaging). The analyses were performed in accordance with the International System for Human Cytogenetic Nomenclature (ISCN).

Cell transplantation and follow-up

The subjects were placed in the prone position and, under local anesthesia, underwent a bone marrow MSC transplantation through percutaneous injection guided by computerized tomography (CT). The injection was performed over a period of 5 min, and 2×10^7 cells were delivered in 1 mL solution. Each patient received one injection of MSCs, performed by a neurosurgeon, at Hospital São Rafael, in Salvador, Bahia, Brazil.

Regular clinical and neurological assessments were performed for 6 months. At each follow-up, a complete clinical assessment, neurological evaluation and AIS scale assessment were conducted. Urodynamic studies, tibial somatosensory evoked potentials (SSEP) and MRI of the spine were performed before transplantation, in the third and sixth months of follow-up.

Clinical pain measures

All pain measurements were performed as previously described [11], in a quiet room with the temperature maintained between 21°C and 23°C. At the time of testing, subjects rated their present pain using an unanchored visual analogue score (VAS). Data from the VAS scale were presented in millimeters. Next, subjects were asked to indicate where they were currently experiencing chronic pain by shading in the areas on a drawing of the dorsal and frontal views of the human body. Following this, subjects were also asked to fill in a standard Brazilian-Portuguese language version of the McGill Pain Questionnaire [22], the results of which were then quantified using the pain rating index [23].

Sensory assessment

For mechanical stimulation, a soft brush (SenseLab Brush 05, Somedic) and von Frey filaments (Touch Test Sensory Evaluator, Stoelting) were used to apply brushing and touch stimuli, respectively. Test sites were identified based on anatomic landmarks to ensure that the same site could be accurately located in subsequent sessions. For each participant, a starting stimulation site was selected based on each individual's level of injury, as determined using the ASIA scale. The starting site was defined as areas at least

Table I. Demographic, clinical and neurological features of the subjects at the time of enrollment.

Subject	Gender	Age (y)	Time after SCI (mo)	SCI level	AIS grade
1	Male	42	25	T10	A
2	Male	51	67	T10	A
3	Male	43	74	T11	A
4	Male	52	111	T9	A
5	Male	36	74	T9	A

four dermatomes above the neurological level of injury, where sensation was expected to be within normal limits. Participants kept their eyes closed and were instructed to report each mechanical stimulus (brush or touch) they perceived with "yes". For each trial, the monofilament (98 mN) was applied perpendicular to the skin surface and, once the filament was fully bent, was held in place for approximately 1 second before being lifted off the skin. Following a positive response, the next area below was stimulated. Brush stimuli was applied continually, from the starting site, until the subjects reported a switch from "yes" (could feel the stimulus) to "no" (could not feel the stimulus).

Urodynamics

The urodynamic study was performed prior to and 3–6 months after the transplantation of MSCs. The following parameters were measured at cystometry: maximum bladder capacity, compliance, bladder sensation and presence of urinary incontinence. Compliance was measured when the bladder showed filling ability >200 mL in the absence of detrusor overactivity. Bladder sensation was marked as absent, reduced, normal or increased. We considered the detrusor leak point pressure the pressure at which urinary leakage occurred in subjects with neurogenic bladder.

Those subjects with micturition were also evaluated with the pressure-flow study. For the urodynamic study, we used Dynamed dynapack mpx 816 equipment. For cystometry, two plastic urethral probes were inserted into the bladder (6 French [Fr] to measure intravesical pressure and 8 Fr for filling). A 10-Fr rectal probe was inserted for measuring intra-abdominal pressure. The filling was done with distilled water at room temperature at a rate of 40 mL/min.

Results

The five volunteers included in the study were all male, with a mean age of approximately 45 years. The demographic, clinical and neurological features of the subjects are presented in Table I.

The phenotypic characterization of MSCs showed 98.2 ± 7.9% of cells positive for CD105, 99.8 ± 0.1% of cells positive for CD73, 99.9 ± 0.05% of cells positive for CD90 and 90.7 ± 7.8% positive for CD44. Moreover, MSC cultures presented 0.3 ± 0.2% of cells positive for CD45, 0.1 ± 0.1% of cells positive for CD11b and 0.3 ± 0.1% of cells positive for CD117. MSCs were able to successfully differentiate into osteocytes and adipocytes.

The intralesional transplantation of MSCs through percutaneous injection guided by CT site was feasible (Figure 1). The procedure was well tolerated and no adverse events associated with the intralesional administration of MSCs by percutaneous injection occurred. A description of the follow-up of each clinical case is reported as follows.

Case 1

The patient is a 42-year-old man with a traumatic SCI in T12 as a result of a gunshot in 2012. At the inclusion evaluation, in 2014, the sensory level was determined at T10 (Table I). On neurological examination, he

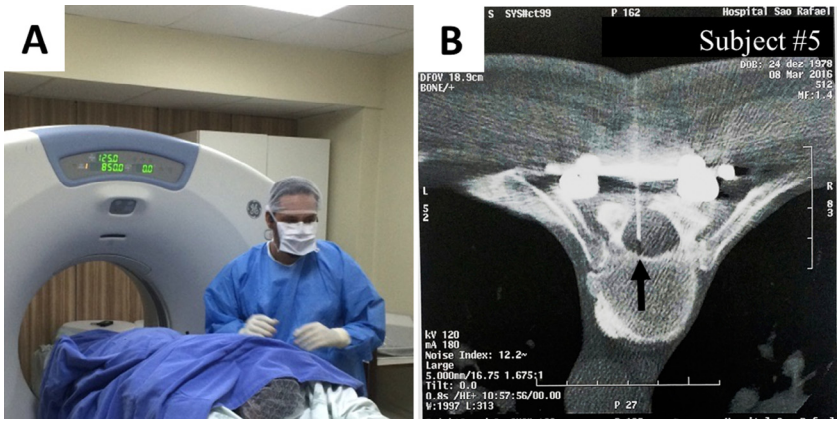

Figure 1. Percutaneous injection of MSCs. (A) Positioning of subject into tomograph. (B) Axial (transverse) image, showing the needle (arrow) reaching the spinal cord.

Table II. Summary of outcome measures.

	AIS grade		FIM score		SCIM	
Subject	Before	After	Before	After	Before	After
1	A	B	114	112	60	63
2	A	A	115	118	60	67
3	A	B/A[a]	112	120	65	75
4	A	A	107	118	62	66
5	A	A	109	118	66	68

[a]Progression to B was reversed at 6 mo after treatment.

presented with flaccid paraplegia of the lower limbs, obliteration of deep and superficial sensation and position sense from the level of T10–T11, absent tibial SSEP and AIS grade of A (no sacral sparing). The patient performed intermittent bladder catheterization, due to absence of bladder-filling sensation and recurrent urinary tract infections. He was able to use a wheelchair and walker, had no pressure ulcers and had neuropathic pain. MRI demonstrated involvement of spinal cord T09–T12 segments. In 2015, he was admitted in the hospital and underwent MSC transplantation.

Within 6 months of follow-up, there were clinical improvements such as changes in AIS grade of A to B (Table II) and in mechanical stimulation response with brush from T11 to T12 (Table III), but not to von Frey stimulation (Table IV). Furthermore,

Table III. Response to mechanical stimulation–SenseLab Brush 05.

	Dermatomes with positive response to brushing stimulation[a]	
Subject	Before treatment	After treatment
1	T11/T11	T12/T12
2	T10/T11	T11/T12
3	T11/T12	T11/T12
4	T9/T10	T11/T11
5	T10/T10	T10/T11

[a]Side of the body (right/left).

Table IV. Response to mechanical stimulation–von Frey filaments.

	Dermatomes with positive response to von Frey stimulation[a]	
Subject	Before treatment	After treatment
1	T10/T11	T11/T11
2	T10/T10	T11/T11
3	T12/T12	L1/T12
4	T9/T10	T10/T10
5	T8/T10	T8/T10

[a]Side of the body (right/left).

Table V. Clinical pain measures.

	VAS (months of treatment)				PRI (months of treatment)			
Subject	0	1	3	6	0	1	3	6
1	5.0	4.3	2.0	3.5	10	16	10	17
2	0	0	0	0	0	0	0	0
3	2.8	0	0	0	8.0	0	0	0
4	0	0	0	0	0	0	0	0
5	10	7	5	8	23	15	21	21

PRI, pain rating index from the McGill Pain Questionnaire.

the patient reported improvement in his sexual dysfunction, urinary bladder-filling sensation and sphincter control. The SCIM score increased from 60–63 points, due to improved dressing independence and regularity of bowel movements, with a slight decrease in FIM score from 114–112, due to bathing and transfer from bed to wheelchair. Neither pain assessments (Table V) nor imaging examination and tibial SSEP showed any significant changes.

Case 2

This patients is a 51-year-old man with history of a traumatic injury of the thoracic spinal cord at T11 level, after a fall from own height in 2009. In 2015, he was included in our protocol and was at T10 sensory level and at A of AIS grade (Table I). Neurologically he had no neuropathic pain, had flaccid paraplegia of lower extremities, absent tibial SSEP, was able to use a walker and wheelchair and needed intermittent bladder catheterization. Evaluation of spinal cord segments between T10 and T12 by MRI was not possible because of artifacts caused by prior surgical procedures.

In July 2015, he underwent autologous MSC transplantation. Imaging examinations did not show any change after the procedure. There was a slight neurological improvement observed during the clinical examination of 30 days after the procedure and it manifested as a change in mechanical stimulation response level from T10 to T11 at the left side. This change persisted until the last evaluation at 6 months, with bilateral improvement in this evaluation (Table IV). Despite the fact that ASIA score did not change, the neurological evaluation of 3 months after the transplantation showed voluntary left fourth toe, fascia lata and bilateral quadriceps contraction. In the third evaluation, the patient declared sensibility at scrotal region. The SCIM score increased from 60 to 67 points, particularly due to improved regularity of bowel movements and FIM score from 115 to 118 points, with reported better transfer from wheelchair to toilet or tub (Table II). No further improvement was noted in other evaluated parameters.

Case 3

A 43-year-old man with SCI at T12 levels, due to a car accident in 2009, was included in our protocol in 2015, presenting with T11 sensory level and classified as AIS A (Table I). MRI of the spinal cord showed a reduction of height T12 body and thickness of medullar cone with myelomalacia and gliosis. Neurologically, he had neuropathic pain, sexual dysfunction, flaccid paraplegia of lower extremities and neurogenic bladder requiring intermittent catheterization. Tibial SSEP evaluation showed severe partial damage.

MSCs were transplanted in August 2015. After transplantation, the patient reported a slight sensibility and thermal sensation in left foot, leg and gluteus. Besides that, he had improved trunk control and neuropathic pain. The urodynamic study changed from low to absence of bladder contraction. There was no change in imaging examinations and in tibial SSEP evaluation. At the first clinical evaluation after the procedure, his AIS grade changed from A to B. This improvement persisted until the last visit (180 days after transplantation), when his ASIA grade returned to A (Table II). The SCIM score increased from 65 to 75 points, attributable to improvement of both sphincter management (bowel and bladder) and bed to wheelchair transfer. FIM score improved from 112 to 120 points, due to better sphincter control and transfers. No further improvement was noted.

Case 4

A 52-year-old man with history of a traumatic injury to the thoracic spinal cord after a fall from height in 2006 was included in our protocol in 2015. His sensory level was T9, and he was classified as AIS grade A (Table I). Neurologically, he had sexual dysfunction, flaccid paraplegia of lower extremities, neurogenic bladder requiring intermittent catheterization, absent tibial SSEP and lumbar pain but no neuropathic pain. MRI demonstrated compressive fracture of T11 body and severe stenosis of spinal cord at this segment with areas of myelomalacia.

MSC transplantation was performed in February 2016. Neither imaging examinations nor AIS grade showed any change during follow-up. Nevertheless, the patient reported better trunk control, improvement of lumbar pain and presented lower vesicoureteral reflux. Moreover, there was an improvement in mechanical brushing stimulation response from T9–T11 (Table III). The SCIM score increased from 62 to 66 points regarding better regularity of bowel movements and his FIM score increased from 107 to 118 points, especially regarding independence of dressing lower body and use of toilet, in addition to that showed an improvement of transfers from wheelchair to bed and toilet (Table II). No further improvement was noted.

Case 5

A 36-year-old man who suffered a car accident with a traumatic SCI at the age of 30 was included in our protocol in 2015. At the time of enrollment, he presented a neurological level of T9. Neurological examination showed flaccid paraplegia of the lower limbs, spasticity episodes, absent tibial SSEP, obliteration of deep and superficial sensation and position sense from T8–T10 levels and AIS grade A (Table I). The patient needed intermittent bladder catheterization because he did not have urinary bladder-filling sensation. He was able to use a wheelchair, had neuropathic pain and sexual dysfunction. A follow-up MRI showed fracture of T8 and T9 bodies with signs of post-traumatic myelopathy.

MSC transplantation was performed in March 2016. There were no adverse events related to the procedure. During follow-up assessments, there were no changes in imaging examinations or tibial SSEP response. Clinically, his AIS grade remained A with a regression of neurological level from T9–T7. Furthermore, deep and superficial sensation did not improve (Tables III and IV). On the other hand, the patient reported better trunk control. The SCIM score increased from 66 to 68 points regarding better bowel and bladder regularity. FIM score improved from 109 to 118 points, due to reported better self-care (bathing, dressing and grooming) and transferring in or out of wheelchair. No further improvement was noted, except for a slight decrease in pain (Table V).

Discussion

During the past decade, pre-clinical and clinical studies have brought evidence supporting the safety and potential benefits of cell-based therapies for SCI, reporting different degrees of neurological recovery [11,20,21,24–27]. The protocols applied in the clinical studies so far have been heterogeneous in terms of manufactory procedures, dose and administration route. Regarding the administration route, our group has been focusing on intralesional administration of MSCs from pre-clinical to clinical studies [11,20,21]. In the present study, we reported the results of our effort to reduce the invasiveness of our protocol for intralesional delivery of MSCs.

Intralesional injection of stem cells offers the advantage of being associated with increased cell engraftment at the injury site compared with the intrathecal route [28]. Homing to the injury site is unlikely to extensively occur in the chronic phase of SCI, after intravenous or intrathecal injection of cells, due to diminished inflammatory signals [24].

It is not established, however, whether the level of cell engraftment associates with the therapeutic efficacy of MSC-based therapies, and recent studies using intrathecal injections also reported positive clinical results [25,29].

Previously, we demonstrated that intralesional transplantation of MSCs performed in open surgery was safe and was associated with neurological improvements in subjects with chronic complete SCI [11]. The only adverse event detected was spinal fluid leakage, which was associated with laminectomy, in one subject. Here we reported the results of a phase 1 pilot clinical study that supports the safety and feasibility of intralesional transplantation of MSCs performed through CT-guided percutaneous injection. This procedure is less invasive and has a decreased cost. Furthermore, in all cases, it could be performed successfully and with no adverse event associated. Importantly, the procedure comprised a decreased length of hospital stay, when compared with our former protocol. Our results are in accordance with a previous study, which was the first to compare CT-guided percutaneous and open surgery for cell delivery in subjects with SCI [26].

Of the two subjects that improved AIS grade to B, incomplete injury, one returned to grade A before the end of the study. A possible reason for the worsening of AIS grade is that chronic SCI subjects may need multiple administrations of cells to have improved results [30]. Available data confirms that adults with chronic SCI have shown better improvement with four implantations of olfactory ensheathing cell (OES) therapy than with a single round [31,32]. Although in our study we did not investigate the use of repeated MSC administrations, two recent studies showed that repeated CT-guided percutaneous injection is feasible and free of adverse events other that neuralgia in a small percentage of the subjects [26,33].

In the present study, the patients showed improvements in SCIM III and FIM scale scores after treatment, which suggests a lower degree of disability. Specifically, all subjects improved bowel regularity after transplantation. This is a significant finding that was also reported by two recent clinical studies with MSCs [25,29]. It is known that an improvement of at least four points of the total SCIM III is needed to obtain a small significant clinical improvement and of ten points to obtain a substantial improvement [34]. According to that, our study showed that MSCs resulted in a clinical significant increase in SCIM III in three subjects (60%).

By evaluating the functional loss of cutaneous sensibility, it was possible to demonstrate that 60% of subjects showed improved sensitivity to tactile stimulation after transplantation of MSCs. The methods of von Frey and brush 05 for the measurement of skin sensitivity have been validated extensively as a protocol to assess somatosensory function in patients with SCI [35,36].

There is a growing body of evidence that demonstrates that, in subjects living with SCI, the determination of minimal clinically important difference (MCID) is as important as the minimum detectable difference (MDD), which determines the smallest real change in outcome, beyond error [37]. MCID is defined as the smallest difference that SCI subjects perceive as beneficial, not necessarily statistically significant. In our study, subjects had many gains regarding pain, trunk control and some minor degree of motor improvement, which can be considered as MCID and of great importance to subjects living with SCI [37]. These results suggest that, even without improvement in AIS grade, MSC therapy can offer many small, but significant, benefits to subjects living with SCI.

In conclusion, autologous bone marrow MSC transplantation, performed through CT-guided percutaneous injection, was shown to be safe and feasible. Further work is needed to demonstrate its potential efficacy.

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