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Review

Mesenchymal Stem Cell Applications in Spine Disorders: A Comprehensive Review

Alice Baroncini [1,2,*], Jörg Eschweiler [1,†], Philipp Kobbe [1], Valentin Quack [1], Samir Smajic [3], Per Trobisch [2], Frank Hildebrand [1] and Filippo Migliorini [1,†]

1 Department of Orthopaedics, Trauma and Reconstructive Surgery, RWTH Aachen University, 52074 Aachen, Germany; joeschweiler@ukaachen.de (J.E.); pkobbe@ukaachen.de (P.K.); vquack@ukaachen.de (V.Q.); fhildebrand@ukaachen.de (F.H.); fmigliorini@ukaachen.de (F.M.)
2 Department of Spine Surgery, Eifelklinik St. Brigida, 52152 Simmerath, Germany; per.trobisch@artemed.de
3 Department of Orthopaedic and Trauma Surgery, St-Josef-Krankenhaus, 52441 Linnich, Germany; samir.smajic@ct-west.de
* Correspondence: alice.baroncini@gmail.com; Tel.: +49-0241-80-35529
† The authors equally contributed to the manuscript.

Featured Application: Current and potential applications of mesenchymal stem cells for the management of spine disorders.

Abstract: Mesenchymal stem cells (MSCs) are increasingly being employed in a number of orthopedic settings, in particular in the treatment of hip and knee osteoarthritis. Recently, the use MSCs has been investigated for different spine settings. However, the use of these cells is not yet widespread in the clinical practice. The aim of this review was to investigate the current literature regarding the use of MSCs in different spine conditions and discuss possible future applications. In particular, degenerative disc disease is the most studied field for MSC application, and is the only one that has already reached the clinical practice, albeit not routinely. Spinal cord injuries are another extensively investigated use of MSCs: despite encouraging preliminary results, a consensus on the efficacy of stem cell therapy for spinal cord injuries has not yet been reached, and their use is still only experimental.

Keywords: spine; degenerative disc disease; Spinal Cord Injury; mesenchymal stem cells

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1. Introduction

Mesenchymal stem cells (MSCs) are increasingly being investigated in a number of different musculoskeletal conditions. MSCs have been investigated for osteoarthritis and chondral defects of the knee, ankle, and hip joints [1–5]. Similarly, MSCs have also been considered for the prevention and management of non-union or critical bone defects, but the data are not yet sufficient to determine their efficacy in these settings [6–8]. Recently, a growing interest for MSC application in spine disorders has been reported. Evidence on this topic is still limited. Previous studies have focused on intradiscal injections of MSCs for degenerative disc disease or for the treatment of spinal cord injuries [9,10]. The present review investigated the current available evidence, discussing pitfalls and future frontiers of MSC applications in spine settings.

2. Intradiscal Injections

Degeneration of the intervertebral disc is a common process which may lead to disability and lower back pain [11]. The socioeconomic burden caused by lower back pain is considerable, as this is the musculoskeletal disorder causing the highest health care expenditures [12]. The standard of care is represented by pharmacological, physical, and infiltrative therapy, followed by surgery when the symptoms cannot be controlled or neurological deficits arise [9,13–15]. However, available therapies are prone to side effects and

complications, increasing the demand for new management options [9]. Intervertebral disc degeneration is accompanied by a quantitative and qualitative degeneration of the nucleus pulposus, along with an alteration of the biomechanics and homeostatic processes [9,16]. MSCs are believed to promote cell differentiation and chemotaxis and to modulate the immune reaction to reduce pain and disabilities related to discal degeneration.

2.1. Clinical Outcomes

Eleven original studies on the intradiscal injection of MSCs are currently available: two randomized control trials (RCTs), eight prospective studies, and one retrospective study. One study was conducted on patients who previously underwent discectomy at the treated level [17]. All other investigations only included patients with a history of chronic lower back pain and clinical findings consistent with discogenic origin of the symptoms, with failed conservative therapy and no previous surgeries at the level of the treated disc [18–25]. A summary of the included articles is presented in Table 1.

In 2006, Haufe and Mork [17] published the first prospective study on 10 patients (5 males and 5 females, aged 32–74 years) who underwent intradiscal injections of hematopoietic stem cells (HSCs) for discogenic back pain. All of the included patients had previously undergone endoscopic discectomy. The HSCs were obtained from the iliac crest (bone marrow aspirate), and 1 mL of HSCs was injected into the problematic disc. The treatment was followed by 2 weeks of hyperbaric oxygen therapy to improve the oxygen content of the disc space, which is known to be a district with limited blood flow. At a 12-month follow-up, none of the patients experienced an improvement of pain measured with the visual analogic scale (VAS), and 90% of the subjects proceeded with surgical treatment. The negative outcomes obtained by Haufe and Mork potentially resided in the patient selection; all of the treated individuals underwent discectomy prior to treatment, which may have impaired the results. In fact, MSCs are not capable of recreating the nucleus pulposus once this has been extruded (e.g., due to herniation) or surgically removed, as was the case in the presented cohort [9]. Recently a retrospective study by Wolff et al. was published [18], reporting the results of intradiscal bone marrow-derived MSC transplantation in 33 patients (19 men, 14 women, mean age of 45 years) suffering from lower back pain. At a 52-week follow-up, positive outcomes in terms of pain and disability were observed; 39% of the patients had an improvement in the VAS of at least 50%, and 31% reported an improvement of at least 50% in the Oswestry Disability Index (ODI). The results of seven prospective studies have been analyzed in a recent meta-analysis [9]. The study included one RCT [23] and six prospective studies [20–22,24–26]. The meta-analysis investigated data obtained from 98 patients with a mean age of 44 years. The MSCs were obtained from bone marrow aspirate in most studies, while Kumar et al. [20] performed transplantation from adipose derived stem cells. Pettine et al. performed transplantation of centrifuged bone marrow aspirate [26], while all other authors performed a culture of the harvested cells before reinjection. Overall, significant improvements in both disability and pain scores were observed at a 1-year follow-up, with the ODI improving by 21% and the VAS by 30%. Pettine et al. [19] successively published the 3-year follow-up of the cohort presented in 2015. At this time point, the authors observed a significant improvement in the ODI and VAS scores compared with the baseline. Six out of 26 patients underwent surgery, but only one of them reported an improvement in the clinical and functional situation in comparison with the baseline at the beginning of the study. Recently, Amirdelfan et al. published the results of an RCT comparing the outcomes of the injection of different amounts of allogenic, in vitro expanded MSCs (6 and 18 million) with hyaluronic acid (HA), with the outcomes obtained with HA alone or a saline solution [11]. Of the 100 involved subjects, those in the saline solution arm presented a higher rate of necessity for post-treatment intervention than patients in the 18 million MSCs group. The 18 million MSCs group scored best in terms of the VAS and ODI at all follow-ups (12, 24, and 36 months), obtaining results better than the other treatment arms (6 million MSCs and HA). However, no significant radiographic improvement was observed in any of the studied cohorts.

Table 1. Summary of the characteristics of the available studies. MSC: mesenchymal stem cells; VAS: visual analogic scale; ODI: Oswestry Disability Index; SF-36: Short-Form 36; MRI: magnetic resonance imaging; CT: computed tomography.

	Author	Year	Journal	Study Design	N. of Patients	Source of MSCs	N. of MSCs	Outcomes of Interest	Follow-Up
1	Haufe et al.	2006	*Stem Cells Dev.*	Prospective	10	Hematopoietic stem cells from iliac crest bone marrow aspirate	/	VAS, requirement for other treatment	1 year
2	Yoshikawa	2010	*Spine*	Case series	2	Hematopoietic stem cells from iliac crest bone marrow aspirate	/	X-rays, CT, MRI	2 years
3	Ozorco et al.	2011	*Transplantation*	Prospective	10	Hematopoietic stem cells from iliac crest bone marrow aspirate	$23 \pm 5 \times 10^6$ MSCs/patient	ODI, VAS, MRI	1 year
4	Pettine et al.	2015	*Stem Cells*	RCT	26	Hematopoietic stem cells from iliac crest bone marrow aspirate	2713 MSCs/mL	ODI, VAS, MRI	1 year
5	Elabd et al.	2016	*J. Transl. Med.*	Case series	5	Hematopoietic stem cells from iliac crest bone marrow aspirate	/	Strength, mobility, MRI	4–6 years
6	Pettine et al.	2017	*Int. Orthop.*	Prospective	26	Hematopoietic stem cells from iliac crest bone marrow aspirate	2 mL (2713 MSCs/mL in average)	ODI, VAS, MRI	1 year
7	Kumar et al.	2017	*Stem Cell Res. Ther.*	RCT	10	Adipose derived stem cells from subcutaneous abdominal tissue	2×10^7 or 4×10^7 MSCs/disc	ODI, VAS, MRI, X-rays	1 year
8	Noriega et al.	2017	*Transplantation*	RCT	24	Allogenic hematopoietic stem cells from iliac crest bone marrow aspirate	25×10^6 MSCs/disc	ODI, VAS, MRI	1 year
9	Singh et al.	2020	*PM R*	Case report	1	/	/	/	/
10	Wolff et al.	2020	*BMC Musculoskelet. Disord.*	Retrospective	33	Hematopoietic stem cells from iliac crest bone marrow aspirate	/	VAS, ODI, SF-36	1 year
11	Amirdelfan et al.	2021	*Spine J.*	RCT	100	Allogenic MSCs	6 or 18 million MSCs	ODI, VAS, MRI, SF-36 and Work Productivity and Activity Index (WPAI)	3 years

2.2. Safety and Complications

The analysis of safety and complications represents a key step when investigating a new therapeutical option. While all of the aforementioned studies reported on complications and adverse events, most authors did not observe any major adverse event correlated to the intervention [18–25]. Three studies reported that a small number of patients experienced lower back pain after the treatment, which either resolved spontaneously or required pharmacological management [19,21,23]. Amirelfan et al. reported discontinuation of the study due to severe pain in 3 out 100 patients, along with one case of infection at the transplantation site [21]. Centeno et al. observed one case of disc herniation in their cohort of 33 patients [21]. Singh et al. reported one case of osteomyelitis and discitis following intradiscal stem cell injection; however, the transplantation procedure had been performed at another institution, and no details were available [27]. Due to the multipotent nature of stem cells, safety concerns exist regarding the possibility that these cells may potentially undergo uncontrolled proliferation or differentiation and thus initiate osteophyte formation [28] or tumorous processes [29,30]. While there are no reports concerning the tumorigenesis potential following the use of stem cells in for orthopedic conditions in the literature, one case of glial hyperplasia has been observed [31]. The patient noticed progressive weakness in the lower limbs accompanied by increasing pain two years after he underwent two intradiscal MSCs injections at two different institutions in Mexico and Russia. No data are available regarding the procedures. The subject underwent a laminectomy and the implantation of an expansile duraplasty without improvement of the symptoms. The patient was known to suffer from multiple autoimmune diseases prior to the MSC transplantation. As no data on the procedure or the kind of stem cells used are available, it is not possible to draw conclusions on the correlation between injection, autoimmune diseases, and the development of glial hyperplasia. It is also possible that the MSCs may have been inadvertently injected intrathecally, as this case resembles a similar complication reported by Hurst after intrathecal MSC administration [32]. This complication highlighted the fact that serious complications are possible, although rare, and particular consideration should be taken when considering MSC management for patients with systemic chronic conditions that may influence the behavior of the cells per se.

2.3. Current Guidelines

Two guidelines have recently been published to aid physicians considering stem cell treatment for chronic lower back pain [16,33]. Based on the available literature, the level of evidence for the use of MSCs in lumbar discogenic lower back pain has been assessed as III [16]. MSCs in musculoskeletal disorders—including spine conditions—have shown to fulfill the criteria of minimal manipulation and homologous use required by national and international regulatory agencies for cell therapy use [33]. Overall, these two criteria require that the processing of the tissue or cells does not alter the relevant characteristics of said tissue or cells, and that recipient tissue or cells exert similar basic functions as the tissue or cells in the donor, respectively. There is also strong evidence that MSC injection is a safe procedure when performed by a trained physician and under sterile conditions and adequate imaging [33].

3. Spinal Cord Injuries

The management of spinal cord injuries (SCIs) represents a challenge, as patients and physicians are confronted with numerous issues ranging from sensory and motor impairment to bed sores [34]. It is estimated that anywhere from 300,000 to 1 million people currently live with chronic SCIs [35,36], and it is thus of paramount importance to investigate possible treatment options to limit the damage to the neural structures after trauma and improve the patients' quality of life after chronic damage has set in [34]. The rationale in the use of MSCs for the treatment of SCIs lies in the known ability of these cells to regenerate damaged nervous tissue [37–39] and in the possibility of these cells to act as scaffold for the regeneration of the lost nervous tissue [40,41]. The stem cells are delivered

intravenously, intraparenchymally, or intrathecally, with or without the use of scaffolds and adjuvants or anti-inflammatory drugs such as minocycline [34,39].

Most available data regard animal studies [42], and the clinical data currently present in the literature are very limited. Recently, seven clinical studies regarding the use of MSCs in patients affected by spinal cord injuries have been published. One clinical trial on four patients with thoracic SCIs treated with midline bilateral human spinal cord-derived neural stem cell injection showed some degree of sensory and motor improvement without any reported adverse events [43]. Two further SCI patients observed a sensory and functional improvement one year after transplantation of MSCs on a collagen scaffold at the injury site [44]. Vaquero et al. reported the results obtained for nine SCI patients treated with intrathecal MSC administration, with an improvement in sensitivity and motor control without any adverse events [45]. In one case report, a patient with an SCI following atlanto-occipital subluxation was treated with intrathecal MSCs harvested from the iliac crest. In this case, no clinical or radiological improvement could be observed [46]. Two further studies assessed the safety and feasibility of MSC therapy for SCIs [47,48], but one was discontinued as the obtained results did not prove sufficient clinical efficacy [47]. A recent meta-analysis established that MSC treatment can improve impairment, sensory scores, and electrophysiological parameters without causing major adverse events [10]. While the data from the available studies are encouraging, there is no consensus on the ideal way to administer MSCs in SCI patients, and the evidence for the effectiveness of this therapeutic approach is still lacking. Currently, 14 clinical trials on the use of MSCs for SCIs are registered on clinicaltrials.gov and will hopefully offer new insight on this topic (status: recruiting).

The key information regarding the available studies is presented in Table 2.

Table 2. Summary of the key data of the available studies. ASIA: American Spinal Cord Injury Association; ISNCSCI: International Standards for Neurological Classification of Spinal Cord Injury.

	Author	Year	Journal	Study Design	N. of Patients	Source of MSCs	MSCs Administration	N. of MSCs	Outcomes of Interest	Follow-Up
1	Chotivichit et al.	2015	*J. Med. Case Rep*	Case report	1	Bone marrow derived mesenchymal stem cells from iliac crest	Intrathecal	30×10^6	ASIA Score, MRI	12 months
2	Curtis et al.	2018	*Cell Stem Cell*	Phase 1 clinical trial	4	Human spinal cord derived neural stem cell (NSI-566)	Stereotactic injection	/	ISNCSCI motor and sensory scores, MRI	18–27 months
3	Xiao et al.	2018	*Cell Transplant*	Prospective Case Series	2	Umbilical cord MSCs on bovine scaffold	Surgical graft into the spinal cord defect	4×10^7	ASIA Score, MRI and nerve electrophysiology	12 months
4	Vaquero et al.	2018	*Cytotherapy*	Phase 2 clinical trial	11	Autologous MSCs from peripheral blood	Intrathecal	100×10^6	ASIA Score, VAS, urodynamic and neurophysiological study	4 months
5	Levi et al.	2018	*Neurosurgery*	Prospective	29	Human central nervous system stem cells	Intramedullary perilesional transplantation	20–40 million	MRI	12 months
6	Levi et al.	2019	*J. Neurotrauma*	Phase 2 clinical trial	12	Human central nervous system stem cells	Intramedullary perilesional transplantation	40 million	ISNCSCI, MRI, pain evaluation	24 months

4. Future Perspectives

Given the increased demand of MSC therapy for spine conditions, the number of preclinical and clinical investigations is exponentially growing. Regarding the management of degenerative conditions, such as intervertebral disc degeneration, the implementation of office-based systems is appealing both for patients and physicians [49], as it may lead to reduction of the discomfort and burden related to hospitalization. This may make MSC management available for a larger number of subjects. Platelet-rich plasma (PRP) has been implemented with positive outcomes for other degenerative spine conditions (e.g., facet joint osteoarthritis) and has been investigated for facet joint, epidural, and sacroiliac joint injections [16]. While the quality of the recommendations for these applications is limited and thus not yet conclusive [16], these may pave the road for the development of MSC injections for spine ailments. Another possible development for intervertebral disc disease may be represented by MSC-derived extracellular vesicles, which seem to modulate inflammation while inducing cellular proliferation and extracellular matrix production [50]. Furthermore, the use of MSCs may be implemented to support spinal fusion surgery and prevent pseudoarthrosis. This complication is developed by 1–2% of patients undergoing spine fusion [51], and these subjects often require revision surgery. Furthermore, MSCs may help improve fusion in stand-alone anterior cervical or lumbar implants [52]. Multiple studies have been conducted to prove that MSCs can induce spinal fusion in animal models [39], and hopefully they will lead the way for future clinical studies.

5. Conclusions

Intradiscal injection of MSCs for degenerative disc ailments is gaining growing interest and broad research. SCIs represent another field in which MSCs have been demonstrated to be a resource to improve clinical outcomes. MSCs are currently investigated mainly in preclinical settings, and their use has not yet become common in clinical practice.

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