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Prospective Study

Evaluation of the Effectiveness of Autologous Bone Marrow Mesenchymal Stem Cells in the Treatment of Chronic Low Back Pain Due to Severe Lumbar Spinal Degeneration: A 12-Month, Open-Label, Prospective Controlled Trial

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Background: Regenerative medicine interventions are applied to assist in the repair, and to potentially replace or restore damaged tissue through the use of autologous/allogenic biologics and it continues to expand. The anti-inflammatory, immunomodulatory, and regenerative properties of bone marrow mesenchymal stem cells (BM-MSCs), and investigation into their therapeutic efficacy and safety in patients with severe chronic low back pain, have not been demonstrated in controlled studies. Multiple pain generators have been hypothesized to be responsible in severe spinal degeneration and it is difficult to identify a single pain generator; consequently, resulting in inadequate therapeutic results.

Objectives: The study was undertaken to evaluate the effectiveness of autologous bone marrow MSCs in the treatment of chronic low back pain due to severe lumbar spinal degeneration with involvement of multiple structures.

Study Design: Prospective, open-label, nonrandomized, parallel-controlled, 2-arm exploratory study.

Setting: A private, specialized, interventional pain management and regenerative medicine clinic.

Methods: The treatment group patients received a one-time bone marrow concentrate injection into spinal structures (i.e., discs, facets, spinal nerves, and sacroiliac joints), along with conventional treatment, whereas, the control group received conventional treatment with nonsteroid anti-inflammatory drugs, over-the-counter drugs, structured exercise programs, physical therapy, spinal injections and opioids, etc., as indicated.

Outcomes Assessment: Outcomes were assessed utilizing multiple instruments, including the Oswestry Disability Index (ODI), Numeric Rating Scale (NRS-11), EuroQOL 5-Dimensional Questionnaire (EQ-5D-3L), Global Mental Health (GMH), and Global Physical Health (GPH). Multiple outcomes were assessed with primary outcomes being minimal clinically important differences (MCID) in ODI scores between the groups and/or a 2-point reduction in pain scores.

In the study group, total nucleated cells, colony forming units-fibroblast, CD34-positive cell numbers and platelets were also recorded, along with post-procedure magnetic resonance imaging changes. Outcomes were assessed at 1, 3, 6, and 12 months.

Results: Significant improvement was achieved in functional status measured by ODI, pain relief measured by NRS-11, and other parameters measured by EQ-5D-3L, GMH, and GPH, in the study group relative to the control group at all time periods. The results showed significant improvements at 12-month follow-up with 67% of the patients in the study group achieving MCID utilizing ODI

when compared to 8% in the control group. Greater than 2-point pain reduction was seen in 74% of the patients at 3 months, 66% of the patients at 6 months, and 56% of the patients at 12 months. Both MCID and pain relief of 2 points were significantly different compared to the control group. Opioid use decreased in the investigational group, whereas, there was a slight increase in the control group. Age, gender, opioid use, and body mass index did not affect the outcomes in the stem cell group.

Limitations: Single center, nonrandomized study.

Conclusions: The first available controlled study utilizing BM-MSCs in severe degenerative spinal disease with interventions into multiple structures simultaneously, including disc, facet joints, nerve roots, and sacroiliac joint based on symptomatology, showed promising results.

Key words: Low back pain, spinal degeneration, disc, facet joint, sacroiliac joint, regenerative medicine, autologous, bone marrow mesenchymal stem cells

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Low back pain is the most expensive medical condition in the United States with an annual expenditure of $134.5 billion in 2016, surpassing diabetes ($114.2 billion), ischemic heart disease ($89.3 billion), and hypertension ($79.0 billion) (1). Furthermore, low back pain causes more global disability than any other condition (2), with 50% to 80% of adults experiencing it at some point in their life, with adults of working age being most vulnerable group of low back pain (3). A global review of the prevalence of low back pain in the adult general population has shown its point prevalence to be approximately 12%, with a one-month prevalence of 23%, a one-year prevalence of 38%, and a lifetime prevalence of approximately 40% (3,4).

The health care costs have been overwhelming with a major burden on the economy of the US leading to the implementation of various health care reform measures, regulations, and to the imposition of guidelines, which have often been based on public policy priorities to reduce health care costs (5-12). Parallel to the increasing disability and health care costs, there has been escalating growth of various modalities for the treatment of chronic low back pain, including over-the-counter (OTC) medications, structured exercise programs, physical therapy, drug therapy, interventional techniques, and surgical interventions. Among these modalities, regenerative medicine therapy as an interventional modality has been added in recent years. Regenerative medicine is based on the process of replacing, engineering, or regenerating human cells, tissues, or organs to restore or establish normal function (13,14). Consequently, regenerative medicine incorporates biomedical, biochemical, and biomechanical technologies to improve cellular migration, replication, and modeling. In fact, the American Society of Interventional Pain Physicians has developed guidelines on performing regenerative medicine procedures and also a position statement on bone marrow concentrate (BMC) injections for musculoskeletal and spinal use (13,14). Systematic reviews (15-19) have shown the value of cellular spinal injections incorporating lumbar disc injections, epidural injections, facet joint injections, and sacroiliac joint injections. However, the evidence has been variable with highest evidence being presented for lumbar disc injections at Level III, whereas, epidural injections, facet joint injections, and sacroiliac joint injections showed Level IV evidence. Few studies (20,38-40,78,80,82) have evaluated the role of autologous and allogeneic (culture expanded) bone marrow mesenchymal stem cells (BM-MSCs) in managing spinal pain with disc injections. The utilization and effectiveness of numerous interventions has been published in multiple manuscripts in recent years (6,7,13,14,21,22,24,25) with no single therapy providing a definitive therapeutic or curative effect in managing chronic low back pain.

The Department of Health and Human Services published a document on best practices in pain management, which included interventional pain management techniques (26,27). In addition to the multitude of issues in managing chronic low back pain, the COVID-19 pandemic and the opioid crisis have affected chronic pain sufferers more significantly than others (28-34). With reduced access resulting from the pandemic, multiple modifications in the management have been made, along with expansion of use of MSCs beyond management of low back pain with treatments utilized in managing COVID-19 (35-37). Thus, with their anti-inflammatory, immunomodulatory, and regenerative properties, MSCs may have the ability to manage or mitigate chronic low back pain. Clinical effects were shown in a study by Pettine et al (38-40) with reports of positive outcomes

in patients with severe chronic low back pain with administration of BMC through a 5-year follow-up. They included patients who were eligible for lumbar fusion in the study and treated them with intradiscal BMC and reported clinical improvement with no adverse effects. Additionally, in a human trial, injected intradiscal bone marrow stem cells survived, proliferated, differentiated, and secreted collagen and extracellular matrix despite the avascular intradiscal environment, which is also hypoxic, acidotic, and hypoglycemic (41). MSCs derived from bone marrow is an attractive biological option for the autologous, safe, and Food and Drug Administration (FDA) compliant administration (14). In contrast, other sources of MSCs, either adipose, allogenic, culture-expanded, or other nonhomologous, continue to lack the FDA compliance (42,43).

Multiple structures in the low back have been described to be able to elicit specific pain patterns. However, structures proven to cause pain by precision diagnostic blocks include disc, facet joint, sacroiliac joint, and spinal nerves, whereas, degenerative disc disease is diagnosed by imaging. Based on precision diagnostic blocks, Manchikanti et al (44), Schwarzer et al (45-47), and DePalma et al (48) have shown the prevalence of internal disc disruption or discogenic pain in 26% to 42% of the patients, facet joint pain in 15% to 40% of the patients, and sacroiliac joint pain in 2% to 18% of the patients. However, they were still unable to account for all back pain based on the precision diagnostic blocks and imaging findings. Consequently, it is postulated that multiple structures are involved in the degenerative process as described by Kirkaldy-Willis et al (49) with 3 joint degeneration hypothesis. Thus, we rationalized that treating all painful structures at one time will be appropriate, specifically for regenerative medicine procedures, as these procedures are not covered by any type of insurance and patients have to be able to pay individually. Thus, a one-time cost may be more attractive and feasible than multiple treatments and multiple charges.

The present prospective controlled trial was undertaken to assess the effectiveness and safety of BM-MSCs injected simultaneously into multiple structures to address multiple pain generators.

Methods

Study Design

This is a prospective, open-label, nonrandomized, parallel controlled, 2-arm exploratory study conducted utilizing the Strengthening the Reporting of Observational Studies in Epidemiology statement (50) and methodology described for evidence synthesis for interventional techniques (51). Approval was obtained from the Institutional Review Board Regen_003-1018-Interventional Spine Specialists. Clinical protocol was registered at www.clinicaltrials.gov [NCT04559295].

Objectives

The study is undertaken to evaluate the effectiveness of autologous MSCs in the treatment of chronic low back pain due to severe lumbar spinal degeneration with involvement of multiple structures, including disc, facet joint, nerve root, and sacroiliac joint.

Setting

The study was performed in a private, interventional pain management center, a tertiary referral center.

Patients

Patients were enrolled with informed consent. Eligible patients were offered autologous stem cell therapy. Patients who chose cell therapy and those who participated were enrolled in the study investigational group, while those who did not participate were placed in the control group. Both groups were offered conventional therapy including OTC drugs, prescription drug therapy, nonsteroid anti-inflammatory drugs, structured exercise programs, physical therapy, percutaneous interventions, and opioids, when deemed necessary.

Inclusion and Exclusion Criteria

Inclusion Criteria: Patients more than 18 years, presenting with symptomatic moderate-to-severe low back pain; with or without radicular pain; pain lasting at least 6 months; and failed conservative therapy or interventional therapy or surgery, including fusion, were included.

Exclusion Criteria: Patients with an abnormal neurologic status, including cauda equina syndrome, immunosuppressed individuals with chronic infections or coagulopathy, and severe psychiatric disorder were excluded. Patients with active cancer; bone marrow disorders; immunosuppressive drugs, if they could not suspend use for 4 weeks prior and for 2 weeks after the procedure; and COVID-19 infections within 6 weeks were also excluded.

Pre-Enrollment Evaluation

All patients underwent a preprocedure medical history, and physical examination with a normal neuro-

logic examination. All patients were evaluated with a magnetic resonance imaging (MRI) prior to the procedure. Complete blood count was performed on all study patients to identify any bone marrow abnormalities.

Interventions

The investigational biologic was autologous BMC injected into the discs, facets, sacroiliac joints, and around the spinal nerves.

Bone marrow aspirate (BMA), 54 mL, was collected over 6 mL Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A) or heparin (1,000 U/mL) from the patient's posterior iliac crest. The procedure was performed in an outpatient interventional pain management suite with sedation consisting of intramuscular midazolam (versed) and oral hydromorphone. Patients were in a prone position with surgical sterile preparation during the procedure. Skin and the iliac crest were anesthetized with a total of 10 mL 2% lidocaine. Positioning of the 15-gauge needle in the iliac wing with a drill was performed under continuous fluoroscopy (Fig. 1). Immediately after the bone puncture, needle advancement was stopped. BMA was collected in heparin-rinsed 10 mL syringes (prefilled with 1 mL of ACD-A or heparin) with a rapid, high-pressure pull on the plunger, targeting a collection of 3-4 mL per pull to mimic the techniques of Hernigou et al (52). The second aspiration was done after the needle was further advanced with the drill for approximately 1 cm. Another 3 mL were aspirated as described. After advancing for another 1 cm the third aspirate was obtained. With one bone puncture, 3 aspirations were performed at different depths for a total volume of 10 mL (9 mL BMA and 1 mL anticoagulant). Three separate bone punctures (through the same skin puncture site) were performed on one side and another 3 on the contralateral side. In some patients, all 6 bone punctures were performed on one side. Six iliac puncture sites and 3 aspiration depths each (18 aspiration sites) were required to obtain the final BMA volume (approximately 60 mL including the anticoagulant). This method was incorporated to maximize the extraction of the number of progenitor cells. Bedside, point-of-care centrifugation was used to concentrate the BMA into BMC. The final BMC volume was customized to each individual patient based on the number of structures injected (average BMC volume per patient was approximately 9 mL). In most patients, calcium chloride (1-2 mL at a ratio of 1-1.5 mL/10 mL of 10% calcium chloride to BMC) was mixed with BMC prior to the injection in anticipation of clot formation in situ.

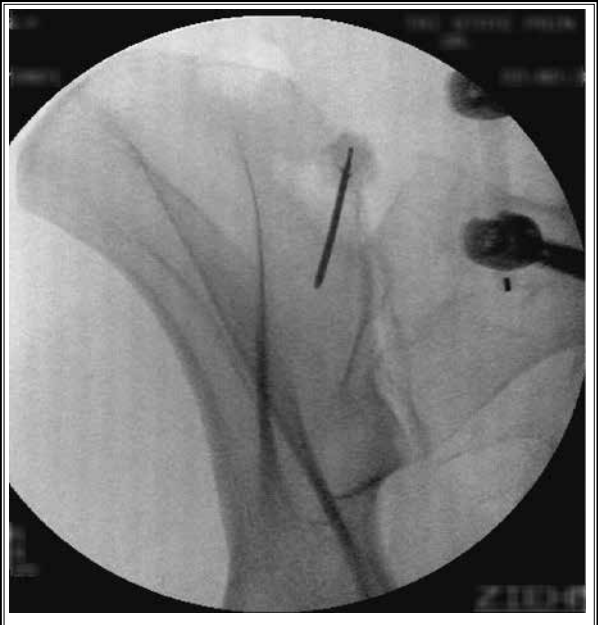

Fig. 1. *Needle placement in the posterior iliac crest.*

Location of pain was the primary determinant for the pain generator selection for BMC administration. Midline pain was treated with intradiscal injections, paracentral pain was subjected to facet injections, and radicular pain was treated with epidural injections. If sacroiliac joint was suspected, it was also injected. Discography or other diagnostic blocks were not performed to identify the pain generator.

Typically, BMC was injected in each disc (2 mL), epidural space (2 mL), facet joints (0.5 mL), and sacroiliac joint (1 mL). If intradiscal access was difficult due to severe disc degeneration or fusion surgery, epidural BMC was injected at that level. In addition, intranuclear injections were not done in patients with disc extrusion, instead epidural BMC was injected. All intradiscal injections were performed slowly to minimize pressure. Either interlaminar or transforaminal approach was adopted for epidural injections (Figs. 2 and 3). If patients had annular tears or if the disc was contacting the nerve, 1 mL was injected intranuclearly and 1 mL into the annulus. Contrast was not used to confirm intranuclear placement; however, it was used to identify the annulus. Omnipaque 240 was diluted 1:1 with preservative-free normal saline. A single dose of prophylactic antibiotics intravenously (cefazolin 2 g or clindamycin 900 mg) and oral antibiotics (cephalexin 750 mg tid or sulfamethoxazole 800 mg/trimethoprim

160 mg bid) for 10 days were administered. Intradiscal antibiotics were not used.

Cellular Analysis

For cell characterization, 1 mL BMA and 0.5 mL BMC samples were analyzed for total nucleated cells (TNC), colony forming units-fibroblast (CFU-F, an indicator for MSCs), CD34-positive (CD34+) (hematopoietic progenitors), and platelet counts. TNC counts were determined via light microscope and hemocytometer following 4',6-diamidino-2-phenylindole staining. CFU-F frequency was determined by in vitro culture of 100 µL BMA and BMC in a 25 cm^2 flask with 5 mL medium containing 10% fetal bovine serum and 1% antibiotics (by volume), incubated at 37°C with 5% carbon dioxide. Complete medium was exchanged after 5 days. Colonies were scored as CFU-F at days 5 and 10, if they demonstrated no fewer than 10 cells with fibroblast morphology. CD34+ frequency was determined by flow cytometry after staining 10 µL BMA and BMC samples with 5 µL fluorescein isothiocyanate-human CD34+ antibody and run in a Beckman Coulter Cytoflex S platform (488 nm excitation, 525 nm emission). All samples were gated based on isotype (negative) controls.

Outcomes

Outcomes were assessed utilizing multiple instruments, including the Oswestry Disability Index (ODI), Numeric Rating Scale (NRS-11), EuroQOL 5-Dimensional Questionnaire (EQ-5D-3L), Global Mental Health (GMH), and Global Physical Health (GPH). Outcomes were assessed at predefined intervals of 3, 6, and 12 months. Primary outcome measures were achievement of minimal clinically important differences (MCID) and minimum of 2-point change on the pain rating scale. MCID often described as "the smallest difference in the score in the domain of interest, which patients receive as beneficial and would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient's management" (53). MCID was defined as a 10-points decrease from baseline for ODI (53). In fact, a recent assessment (54) of criteria for failure and worsening after surgery for lumbar spinal stenosis in a spine registry showed ODI derivates were most accurate to identify both failure and worsening after surgery for degenerative lumbar spinal stenosis. They showed that less than a 10-point improvement in ODI most accurately identified failure. The other outcomes were measured by EQ-5D-3L, GMH, GPH, and also included opioid intake.

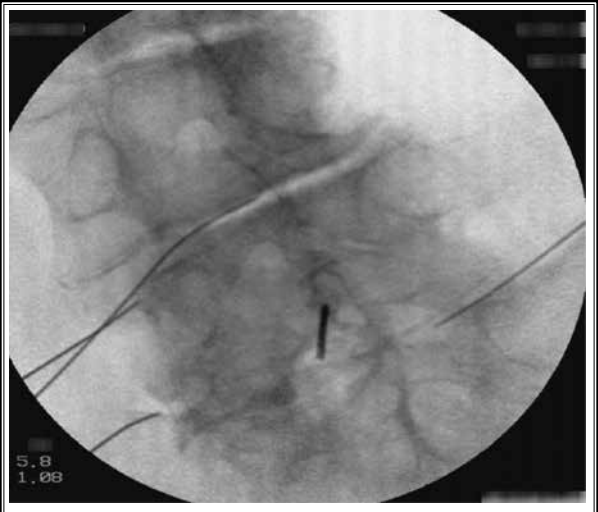

Fig. 2. *AP view of needle placement in L4/5, L5/S1 discs, left L4/5, L5/S1 facets, and left L5/S1 interlaminar epidural space.*
AP, Anteroposterior.

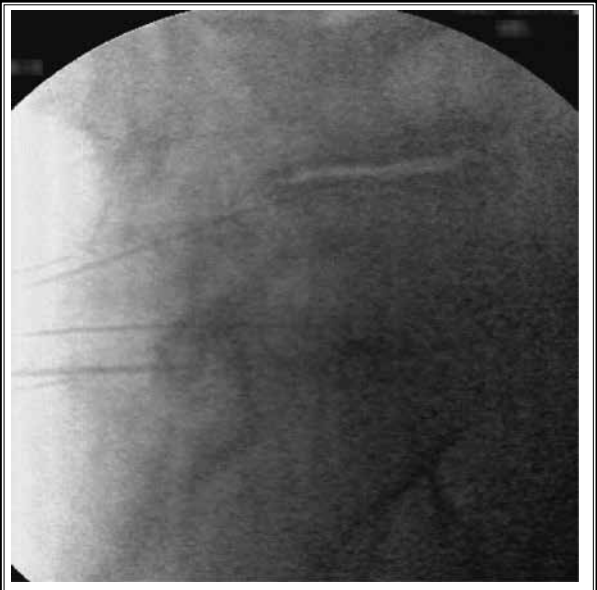

Fig. 3. *Lateral view of needle placement in L4/5, L5/S1 discs, left L4/5, L5/S1 facets, and left L5/S1 interlaminar epidural space.*

Based on the ODI scores, 0% to 20%: minimal disability; 20% to 40%: moderate disability; 40% to 60%: severe disability; 60% to 80%: crippled; 80% to 100%: bedbound or exaggerating their symptoms (55,56).

The value and validity of NRS-11 (57) and ODI (53-56) have been described. The NRS-11 pain scale 0-10

and functional assessment using the ODI 0-50 scale were measured. Opioid intake was calculated in each patient by conversion into morphine equivalent dosages (58).

EQ-5D-3L is a standardized measure of health-related quality of life with 5 dimensions, each having 3 response levels of severity (59). The level of severity is measured as: 1: indicating no problems; 2: indicating some problems; and 3: indicating extreme problems. EQ-5D-3L has been extensively reported in over 8,000 peer-reviewed papers over the past 30 years (60).

GMH (61,62) is an assessment tool utilized extensively to measure mental health.

GPH (62) assess overall health with ratings of 5 primary domains (physical function, fatigue, pain, emotional distress, and social health), as well as perceptions of general health that cut across domains. The responses include excellent, very good, good, fair, and poor.

Statistical Analysis

Descriptive statistics with mean and standard deviation was performed. The normality of data distribution was tested by the Shapiro-Wilk test. Analysis of variance (ANOVA) 2-way for repeated measures, reporting the "F-ratio," degrees of freedom and the "P" value was used to verify the interaction time outcomes and the main effect of time within each group. The test of Mauchly was adopted to verify the sphericity of the data, which, in case of violation, the degrees of freedom would be corrected by the epsilon of Greenhouse-Geisser or Huynh-Feldt.

Partial eta squared (η_p^2) was used to determine the effect size. Post hoc of Bonferroni was adopted for identification of pairs of difference. Binary logistic regression analyses were performed using reduction in ODI data in 2 models; model 1: unadjusted; and model 2: adjusted for gender, age, body mass index (BMI), duration of pain, and additional procedures. The alpha was set at 1% and the software used was SPSS 22.0 (IBM Corporation, Armonk, NY).

Results

Patients

From May 2019 to February 2021, 80 patients in the interventional pain management clinic with chronic low back pain were included after meeting the inclusion criteria with 40 patients in the intervention group and 40 patients in the control group. Four patients in the study group and no patients in the control group dropped out.

Demographic Characteristics

Demographic characteristics are shown in Table 1. Both groups were similar in regards to age, gender, weight, height, duration of pain, baseline pain scores, spinal procedures, nonopioid analgesics, and history of back surgery. However, the BMI and opioid use was higher in the control group, but more patients in the study group had prior history of fusion surgery or laminectomy, severe facet hypertrophy, severe foraminal/central/lateral recess spinal stenosis, neural impingement, annular tears, and arachnoiditis either alone or in combination. For the study purposes, these changes were classified as "significant MRI changes."

Results of Outcomes

The ODI scores of BMC patients were similar at the time of baseline compared to the control group (P = 0.548). Two-way repeated measures ANOVA revealed significantly different ODI score changes (at 1, 3, 6, and 12 months after the procedure) between groups ($F = 5.830$, $P < 0.001$). P values were adjusted using the Bonferroni multiple testing correction method. The effect of treatment was significant after 1 month ($P = 0.001$), 3 months ($P = 0.001$), 6 months ($P = 0.001$), and 12 months ($P = 0.001$). Furthermore, at each time period, the changes in the ODI scores from baseline were significant in the study group alone: 1 month ($P = 0.001$), 3 month ($P = 0.001$), 6 month ($P = 0.001$), and 12 months ($P = 0.001$) (Fig. 4 and Table 2). The pain rating scores are shown in Table 2 and Fig. 4 with significant improvement in mean pain scores from 7.1 ± 2.2 to 4.2 ± 2.8 with significant difference in pain scores from baseline to all follow-up periods. Further, as shown in Table 3, 74% of the patients at 3 months, 66% at 6 months, and 56% at 12 months showed at least a 2-point decrease in pain scores compared to 13%, 15%, and 8% in the control group, consecutively.

Based on MCID criteria, 67.7% of patients in the treatment group achieved MCID through 12 months, compared to only 7.7% of the control group ($P = 0.001$) (Table 4).

Similar trends were also observed in the back pain NRS-11, leg pain NRS-11, EQ-5D-3L, and GPH scores (Table 2). The only exception was noted in the GMH scores. Statistical significance ($P < 0.05$) was seen at all time periods in the study group when compared to the control group; however, this difference was observed only at 1 and 3 months, but not at 6 or 12 months

Table 1. *Demographic characteristics of patients.*

		Study (n = 40)	Control (n = 40)	*P* value
Age in years		61.08	59.05	0.347
Height (cm)		170.66	166.83	0.060
Weight (kg)		89.28	97.73	0.081
BMI (mean)		30.6	35.2	0.006
Duration of Pain (in years)		10.25	11.78	0.528
NRS-11 for Back Pain (baseline)		7.10	6.60	0.259
NRS-11 for Leg Pain (baseline)		5.50	4.90	0.360
Percent of Patients on Opioids		60%	100%	< 0.001
Percent of Patients Receiving Nonopioid Pain Management		58%	65%	0.500
Percent of Patients with Prior Spinal Injections		30%	28%	> 0.990
Percent of Patients with History of Lumbar Surgery		15%	25%	0.400
Percent of Patients with Back Fusion		25%	28%	0.800
Percent of Patients with Prior Laminectomy		27%	15%	0.382
Percent of Patients with Disc Bulge		93%	90%	0.712
Average Number of Each Condition in Each Patient: FH or LRS or FS or SCS, NI, AT, and ARACH		2.05%	1.76%	0.003
Facet Hypertrophy (Percent of Patients)	Severe	20%	3%	0.029
	Moderate	18%	18%	0.769
	Mild	35%	21%	0.211
Lateral Recess Stenosis (Percent of Patients)	Severe	5%	0%	0.494
	Moderate	3%	3%	1.000
	Mild	8%	5%	1.000
Foraminal Stenosis (Percent of Patients)	Severe	28%	13%	0.162
	Moderate	23%	23%	0.789
	Mild	28%	21%	0.599
Spinal Canal Stenosis (Percent of Patients)	Severe	13%	5%	0.432
	Moderate	8%	13%	0.712
	Mild	18%	10%	0.516
Neural Impingement (Percent of Patients)		48%	31%	0.169
Disc	Degeneration	48%	46%	0.304
Disc	Annular Tear	25%	5%	0.028
Disc Height (Reduction Percent of Patients)	Severe	5%	3%	1.000
	Moderate	0%	3%	1.000
	Mild	20%	5%	0.091
Arachnoiditis (Percent of Patients)		3%	0%	1.000

$\alpha = 0.05$

Abbreviations: NRS-11, Numeric Rating Scale; FH, Facet Hypertrophy; LRS, Lateral Recess Stenosis; FS, Foraminal Stenosis; SCS, Spinal Canal Stenosis; NI, Neural Impingement; AT, Annular Tear; ARACH, Arachnoiditis.

when compared to baseline in the study group (Table 2). Based on the ODI scores at 12 months, 10 patients in the control had higher scores than baseline compared to only 5 in the study group.

Opioid Intake

More patients in the control group were on opioids compared to the study group (100% vs 60%; *P* = 0.001). At the end of the study period (12 months),

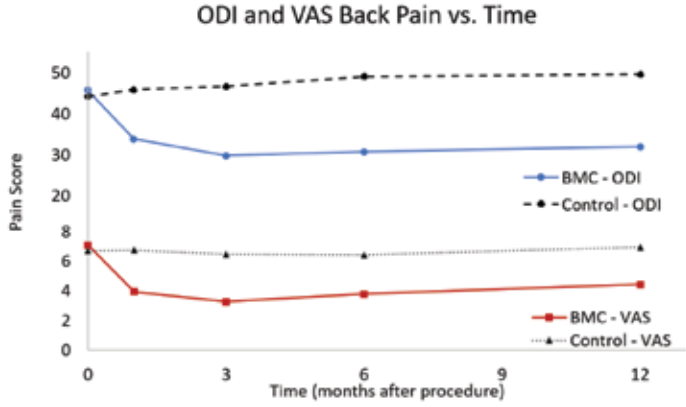

Fig. 4. *Improvement in ODI and VAS scores in the study group compared to the control group.*
ODI, Oswestry Disability Index; VAS, Visual Analog Score.

among 22 patients in the treatment group, 8 patients did not require opioids and 9 patients decreased opioid use. One patient who was not on opioids before the procedure required opioids at the 12-month follow-up. In contrast, all patients in the control group remained on opioid therapy throughout the study period.

Correlation of Outcomes with Imaging

In the study group, after 6 months, post-procedure MRIs were obtained for 15 patients. In 6 patients, very subtle increases were seen in the T2 signal in the discs (40%). In 9 patients, no MRI changes were observed (60%). MRI changes did not correlate with

Table 2. *Outcome data for ODI, NRS-11, EQ-5D-3L, GMS, and GPH scores.*

	Group	Baseline	1 Month	3 Months	6 Months	12 Months	Main Effect		
							Time	Group	Time* Group
ODI Score	Study Group	46.1 ± 12.6	33.4# ± 15.4	28.8# ± 17.1	29.9# ± 16.5	31.1# ± 18.9	F = 5.830 $P < 0.001$ $n_p^2 = 0.08$	F = 20.17 $P < 0.001$ $n_p^2 = 0.22$	F = 15.23 $P < 0.001$ $n_p^2 = 0.18$
	Control Group	44.3 ± 13.0	45.9* ± 14.6	47.3* ± 15.4	48.9* ± 14.5	49.5* ± 14.3			
NRS-11 for Back Pain	Study Group	7.1 ± 2.2	3.8# ± 2.3	3.1# ± 2.5	3.7# ± 2.4	4.2# ± 2.8	F = 14.981 $P < 0.001$ $n_p^2 = 0.17$	F = 39.252 $P < 0.001$ $n_p^2 = 0.36$	F = 18.125 $P < 0.001$ $n_p^2 = 0.20$
	Control Group	6.6 ± 1.7	6.8* ± 1.7	6.9* ± 2.0	6.6* ± 2.3	7.1* ± 2.0			
NRS-11 Leg Pain	Study Group	5.5 ± 3.2	3.0# ± 2.7	2.5# ± 2.9	2.9# ± 2.8	3.1# ± 3.1	F = 2.859 $P < 0.025$ $n_p^2 = 0.04$	F = 17.32 $P < 0.001$ $n_p^2 = 0.20$	F = 7.43 $P < 0.001$ $n_p^2 = 0.1$
	Control Group	4.9 ± 2.6	5.1* ± 2.9	5.7* ± 2.9	5.6* ± 2.9	5.5* ± 3.0			
EQ-5D-3L	Study Group	0.57 ± 0.06	0.66# ± 0.09	0.68# ± 0.10	0.66# ± 0.10	0.66# ± 0.12	F = 5.53 $P < 0.001$ $n_p^2 = 0.07$	F = 11.98 $P < 0.001$ $n_p^2 = 0.14$	F = 16.43 $P < 0.001$ $n_p^2 = 0.19$
	Control Group	0.60 ± 0.09	0.58* ± 0.09	0.58* ± 0.09	0.58* ± 0.08	0.57* ± 0.09			
GMH Score	Study Group	43.2 ± 7.4	47.9# ± 7.0	48.5# ± 8.8	46.3 ± 8.9	46.9 ± 9.9	F = 0.78 $P > 0.52$ $n_p^2 = 0.01$	F = 5.61 $P < 0.021$ $n_p^2 = 0.07$	F = 9.16 $P < 0.001$ $n_p^2 = 0.11$
	Control Group	44.6 ± 7.7	41.9* ± 8.6	41.5* ± 9.4	41.9μ ± 7.8	41.9μ ± 10.1			
GPH Score	Study Group	36.0 ± 4.3	42.3# ± 6.0	44.5# ± 7.3	42.9# ± 8.4	43.1# ± 9.2	F = 7.34 $P < 0.001$ $n_p^2 = 0.09$	F = 18.22 $P < 0.001$ $n_p^2 = 0.20$	F = 15.85 $P < 0.001$ $n_p^2 = 0.18$
	Control Group	37.5 ± 6.1	36.6* ± 6.0	36.1* ± 6.2	36.4* ± 5.5	35.1* ± 6.0			

Abbreviations; ODI, Oswestry Disability Index; NRS-11, Numeric Rating Scale; EQ-5D-3L, EuroQOL 5-Dimensional Questionnaire; GMH, Global Mental Health; GPH, Global Physical Health.

- Statistically significant ($P < 0.01$) with baseline vales within study group.
* - Statistically significant ($P < 0.01$) control group with study group ODI scores.
μ - Statistically significant ($P < 0.05$) control group with study group ODI scores.

Table 3. *Results of changes of back pain NRS-11 with 2-point decrease.*

	At 1 Month		At 3 Months		At 6 Months		At 12 Months	
Back pain NRS-11	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**
< 2 points	34% (23)	92% (35)	26% (10)	87% (34)	34% (13)	85% (34)	44% (17)	92% (36)
>=2 points	66% (25)	8% (3)	74% (28)	13% (5)	66% (25)	15% (6)	56% (22)	8% (3)
P value	0.001		0.001		0.001		0.001	

Abbreviation: NRS-11, Numeric Rating Scale.

Table 4. *MCID in ODI score among the groups (10 points decrease).*

	At 1 Month		At 3 Months		At 6 Months		At 12 Months	
ODI Score	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**
< 10 points	42% (16)	90% (34)	29% (11)	85% (33)	37% (14)	95% (38)	33% (13)	92% (36)
>=10 points	58% (22)	10% (4)	71% (27)	15% (6)	63% (24)	5% (2)	67% (26)	8% (3)
P value	0.001		0.001		0.001		0.001	

Abbreviations: MCID, minimally clinically important difference; ODI, Oswestry Disability Index.

pain relief. Many patients obtained pain relief despite any changes on the MRI, suggesting low back pain results from inflammation rather than mechanics/structure.

Cell Characterization

Cell characterization was performed on BMA and BMC samples for the 40 patients in the study group. The results are provided in Table 5. The average BMA TNC count was 45.5 million/mL. The average volume of BMC injected per patient was 9.1 mL. The average BMC counts for TNC and CFU-F were 239 x 10^6 per mL (total 2.1 x 10^6) and 4,965 per mL, respectively. The average CFU-F frequency in BMC was 0.0021% (~1 CFU-F per 50,000 TNC). The enrichment factor for the various cell types ranged from 4.1x to 5.3x above baseline. Centrifugation-based concentration of BMA reduced hematocrit volume from 35.8% to 24.5%. Changes to clinical outcomes were compared to CFU-F counts and patient age to determine potential effects, but no statistically significant effects were found (Fig. 5). The cell counts in this study for BMA and BMC were much greater than previous studies (38,63-70), and only 8 of 40 patients had fewer than 1,000 CFU-F/mL. Moreover, the low CFU-F/mL counts did not correlate with the BMA/BMC TNC counts, which were in the normal range. CD34+ counts are considered to correlate with the quality of the bone marrow aspiration technique. A median CD34+ content of 1.57% in patients with a median age group of 30 is considered as a good harvest (71). In this study, our BMA CD34+ count was 1.3% in a cohort of patients with a mean age of 61. A high percentage of CD34+ among samples with high TNC counts seems to reflect a good stem cell harvest technique.

Correlation of Multiple Variables

Binary logistic regression analysis adjusted for gender, age, BMI, duration of pain, and additional procedures showed that using an ODI score decrease by at least 10 points from baseline (odds ratio, 16.177; 95% confidence interval: 3.048-85.851; *P* = 0.001) was independently associated with the study group at 12 months after the procedure. Odds ratio without adjusting for gender, age, BMI, duration of pain, additional procedure was 24.0 (95% confidence interval: 6.204-92.851; *P* = 0.001). Additionally, independently it was also shown that "additional procedures" did not influence the positive outcomes seen in the study group (Table 6).

Discussion

The results of this study showed significant improvement in function and pain relief in 67% of the study group, and achieved MCID for ODI at 12 months, when compared to only 8% in the control group. Pain relief was also seen with a 2-point difference in 56% of patients in the study group at 12 months compared to only 8% in the control group. The study group also showed reduced opioid usage. This is the first of its nature study with BM-MSC injecting multiple structures in one setting in chronic spinal degeneration.

Table 5. *Cell analysis of study BMA and BMC samples for average TNC, CFU-F, CD34+, and platelets, and enrichment factor after centrifugation.*

	BMA	BMC	Enrichment
TNC (million/mL)	45.5	239.3	5.2
Total TNC/patient (million)	2,376	2,104	0.88
CFU-F frequency (% per TNC)	0.0026%	0.0020%	0.8
CFU-F/mL	1,220	4,987	4.0
CFU-F/patient	65,880	44,883	0.68
CD34+/mL	601,025	2,840,824	4.7
% CD34+	1.3	1.2	0.92
Platelets (million/mL)	214.5	960.8	4.5
Hematocrit (%)	35.8%	24.5%	0.7

Abbreviations: BMA, bone marrow aspirate; BMC, bone marrow concentrate; TNC, total nucleated cells; CFU-F, colony forming units-fibroblast; CD34+, CD34-positive.

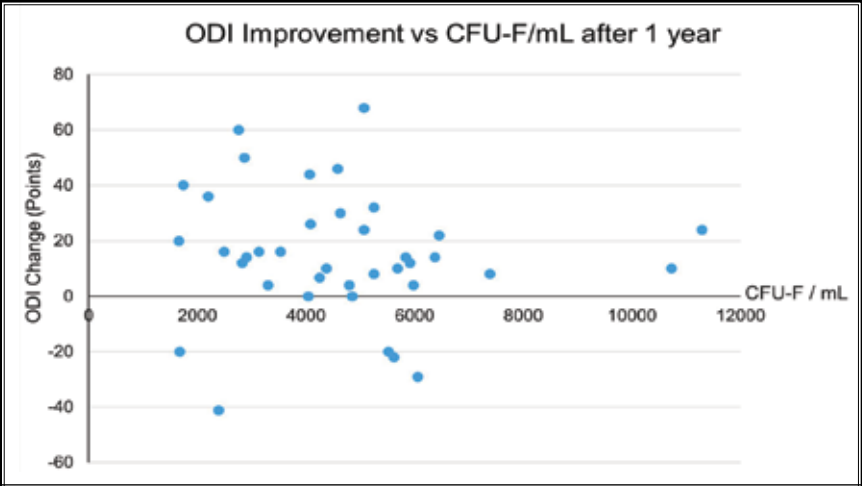

Fig. 5. *Correlation of ODI scores with CFU-F numbers after one year.*
ODI, Oswestry Disability Index; CFU-F, colony forming units-fibroblast.

As opposed to earlier trials, patients in this study were not stringently selected. The goal was to evaluate this therapy in "real life" challenging patients. Patients with severe changes on the MRIs were included as long as they did not exhibit neurologic deficits. Significant MRI changes, such as severe spinal stenosis, severe facet arthropathy, or disc herniations/extrusions were not used as exclusionary criteria if there were no "red flag" neurologic findings. Even procedurally challenging patients who had lumbar fusion surgeries were included. Prior trials for discogenic pain typically included patients with < 50% reduction in disc height, but in this study, the traditionally used < 50% decrease of disc height was not one of the exclusion criteria (some patients with almost 90% reduction were included) as shown in Figs. 2 and 3.

Previous studies (40,63-67,72) have shown the number of MSCs in the autologous, point-of-care BMC correlates positively with clinical outcomes in several orthopedic applications, including lumbar disc disease, knee osteoarthritis, fracture nonunions, avascular necrosis, and rotator cuff repair. In order to maximize the extraction of MSCs, our bone marrow aspiration technique was time consuming and fastidious resulting in higher TNC and CFU-F numbers than previously reported (38,63-70). Because the cell counts in this study were so high, a dose effect was not observed relative to any of the clinical metrics through 12 months

Table 6. *Multivariate analysis of gender, age, BMI, duration of pain, baseline opioids, and additional procedures.*

		B	SE	Wald	df	Sig	Exp(B) Odds Ratio	95% CI for Exp(B)	
								Lower	Upper
Step 1	Group	2.784	0.852	10.686	1	0.001	16.177	3.048	85.851
	Gender	0.105	0.723	0.021	1	0.885	1.111	0.269	4.580
	Age	-0.050	0.035	1.996	1	0.158	0.951	0.888	1.019
	BMI	0.039	0.042	0.861	1	0.354	1.040	0.957	1.130
	Duration of Pain	-0.002	0.004	0.299	1	0.585	0.998	0.991	1.005
	Baseline Opioids (MED)	-0.034	0.039	0.756	1	0.385	0.967	0.895	1.044
	Additional Procedures	1.092	0.750	2.118	1	0.146	2.980	0.685	12.965
	Constant	-0.192	2.496	0.006	1	0.939	0.826		

Abbreviations: BMI, body mass index; CI, confidence interval.

post-therapy. It is important to note that there was no negative clinical impact for the highest cell counts ("overdosing," e.g., TNC > 250 million/mL, CFU-F > 5,000/mL). The impact of bone marrow aspiration technique and concentration (centrifugation) quality cannot be overstated, especially when multiple structures are injected. The technique used in this study resulted in consistently high concentrations of TNC and CFU-F, which are synonymous with MSCs. Poor aspiration and/or concentration results in a biologic that more closely resembles blood or platelet-rich plasma, which could negatively impact clinical efficacy. Even though many study patients had severe spinal degeneration, favorable outcomes were seen presumably because multiple pain generators were injected with high doses of MSCs.

The average age of the study patients was 61. The quantity and quality of BM-MSCs are known to decrease with aging. However, it is known that the reduction of the number of BM-MSCs in the axial skeleton and iliac crests is not as significant as seen in the long bones (67,73). This partially explains the good response observed in elderly patients and the numbers obtained from the iliac crest seem to be clinically relevant. No difference in outcomes was observed between patients who are less than 60 compared to those who are older than 60. Similarly, there was no difference when the cutoff was increased to 65 (Table 7). Furthermore, there was no difference in the outcomes between genders. Although more patients in the control group had a higher BMI and opioid use, these factors did not impact outcomes. Additionally, even though more patients in the investigational group received non-stem cell procedures during the study period, this did not contribute to the positive outcomes seen from the stem cell therapy. Similar to the findings in other studies (38), 60% of patients did not exhibit regenerative changes on the MRI from stem cell therapy; however, positive therapeutic outcomes were observed in these patients.

BM-MSC administration may be opioids sparing in low back pain, as a decrease in opioids utilization was seen in the study group in contrast to the control group, which saw an increase. Moreover, 77% of patients in the investigational group either stopped or decreased opioids compared to none in the control group.

Amongst all new technologies, stem cell therapy seems to be the most promising. There is robust in vitro and animal data (74,75) demonstrating disc regeneration with stem cells. Previous clinical trials (20,38-40,76-82) observed that stem cell therapy can potentially improve pain and function scores in chronic low back pain and more importantly, there were no complications. Additionally, pain relief can be sustained beyond 5 years (40,82).

Although no major complications were noted in this study, the majority of patients reported significant post-procedure pain (i.e., axial low back pain), which lasted from a few days to a week. This pain was most likely associated with re-pressurization of the disc after intranuclear injection. This pain was successfully treated with short-term opioids. No radicular pain flare-ups from epidural BMC were observed.

Our approach of injecting multiple purported pain generators simultaneously is contrary to the traditional "individual pain generator" interventional pain management philosophy. However, multiple studies (83) have shown that low back pain is multifactorial. Furthermore, despite detailed history, physical exam, and advanced imaging, it is difficult to identify the pain generator. Diagnostic blocks, although helpful, are not always accurate due to false positive/false negative responses and placebo effects. We did not employ discograms since their diagnostic capability is controversial. Moreover, there is evidence discograms can accelerate disc degeneration (83). We chose to primarily inject the discs and facets based on the scientific rationale based on multiple studies, which showed that they are the main pain generators in low back pain.

The present study has several limitations. Firstly, since the procedure was not covered by third-party payers, the enrolled study patients had to pay for the procedure resulting in a possible motivational bias to-

Table 7. *Improvement of ODI at 12 months by age group.*

ODI Score	**< 60 years**	**>= 60 years**
< 12%	8% (1)	25% (6)
= 12%	92% (12)	75% (18)
P value	0.122	
ODI Score	< 60 years	>= 60 years
< 30%	38% (5)	54% (13)
>= 30%	62% (8)	46% (11)
P value	0.495	
ODI Score	< 65 years	> 65 years
< 12%	16% (4)	25% (3)
>= 12%	84% (21)	75% (9)
P value	0.5133	
	< 65 years	> 65 years
< 30%	40% (10)	67% (8)

Abbreviation: ODI, Oswestry Disability Index.

ward better outcomes. Secondly, the BMI was higher in the control group. Additionally, this group had higher opioid use at baseline compared to the investigational group although multivariate analysis showed that both these factors did not impact outcomes. However, based on MRI findings, the study group exhibited more severe spinal degeneration compared to the control group. Thirdly, multiple pain generators were injected simultaneously. Additional research needs to be performed to assess if good outcomes can be achieved by addressing fewer structures. Furthermore, a higher number of patients in the study group received non-BMC injections compared to the control group in the follow-up period. However, these procedures did not result in pain relief and hence we do not feel that these interventions were responsible for the positive outcomes we saw in the study group. The small sample size limited our ability to obtain enough clinical data to draw strong conclusions, and future randomized controlled trials with larger sample sizes are required to prove the efficacy of MSCs.

Conclusions

Autologous bone marrow cell therapy represents an alternative to traditional treatments for low back pain to provide pain relief via multimodal MSC functions of anti-inflammation, immunomodulation, cell recruitment, and remodeling/regeneration. Stem cell therapy has the potential to slow, halt, or, in some cases, reverse the progression of degenerative discs and joints. Positive outcomes in this study population, which presented with severe spinal degeneration were likely due in part to the combination of injecting high numbers of progenitor cells/MSCs and by addressing multiple pain generator sites. It appears that stem cell therapy could be a reasonable option to treat chronic low back refractory to conventional treatment, especially if performed by qualified physicians following the proper guidelines (13).

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Author Contributions

The study was designed by SA, KBA, NB, and LM. Statistical analysis was performed by Sagar Vidyasagar Pampati.

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