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ORIGINAL PAPER

Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up

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Abstract
Purpose The purpose of this study is to assess safety and feasibility of intradiscal bone marrow concentrate (BMC) injections to treat low back discogenic pain as an alternative to surgery with three year minimum follow-up.
Methods A total of 26 patients suffering from degenerative disc disease and candidates for spinal fusion or total disc replacement surgery were injected with 2 ml autologous BMC into the nucleus pulposus of treated lumbar discs. A sample aliquot of BMC was characterized by flow cytometry and CFU-F assay to determine progenitor cell content. Improvement in pain and disability scores and 12 month post-injection MRI were compared to patient demographics and BMC cellularity.
Results After 36 months, only six patients progressed to surgery. The remaining 20 patients reported average ODI and VAS improvements from 56.7 ± 3.6 and 82.1 ± 2.6 at baseline to 17.5 ± 3.2 and 21.9 ± 4.4 after 36 months, respectively. One year MRI indicated 40% of patients improved one modified Pfirrmann grade and no patient worsened radiographically. Cellular analysis showed an average of 121 million total nucleated cells per ml, average CFU-F of 2713 per ml, and average CD34+ of 1.82 million per ml in the BMC. Patients with greater concentrations of CFU-F (>2000 per ml) and CD34+ cells (>2 million per ml) in BMC tended to have significantly better clinical improvement.
Conclusions There were no adverse events related to marrow aspiration or injection, and this study provides evidence of safety and feasibility of intradiscal BMC therapy. Patient improvement and satisfaction with this surgical alternative supports further study of the therapy.

Keywords Degenerative disc disease · Intradiscal injection · Mesenchymal stem cells · Bone marrow concentrate

Introduction

The direct and indirect costs of treating pathology related to discogenic back pain in the United States exceed $100 billion annually [1, 2]. The development of disc degeneration in the lumbar spine is almost universal over the age of 50 years. This observation appears related to humans' recent evolution to an upright posture and S-shaped spinal column [3–6]. Treatment options have been limited to conservative care, steroid injections, prescribed opiates, and surgery. The surgical treatment for discogenic back pain has been evaluated by Phillips et al., in a systematic review of studies comparing spinal fusion versus conservative care as well as studies comparing different fusion techniques for discogenic back pain [7]. After establishing strict inclusion and exclusion criteria for the publications, six of 26 reviewed studies reported on prospective randomized studies comparing fusion versus non-surgical therapy in patients with moderate to severe discogenic low back pain. Results showed 35.3% improvement in the surgical group (547 patients) and 20% improvement in the non-surgical group (372 patients). Twelve prospective randomized studies were reviewed comparing various fusion techniques. Minimum follow-up in every study was 2 years. The weighted

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average results in the 12 studies were 43.3% improvement in back pain (1420 patients) with a re-operation rate of 12.5%. Artificial disc replacement has seen an increase in use for degenerative lumbar discs over the past several years as an alternative to fusion. The purported benefits of lumbar artificial disc replacement over fusion surgeries include maintaining lumbar spine range of motion that may reduce adjacent segment degeneration compared to fusion. Six studies compared disc replacement with fusion and found slight, non-significant improvements of 5.2 mm in visual analog scale (VAS) back pain and 4.3 points improvement in Oswestry Disability Index (ODI) scores [8]. These studies, along with others, demonstrate the difficulty in surgically treating discogenic low back pain [6, 9–12].

There has been a number of recent studies researching the potential of biologic based therapies to treat many conditions, including disc degeneration [13–15]. In pre-clinical animal models, groups have demonstrated disc regeneration and rehydration using a specialized cell population known commonly as mesenchymal stromal/stem cells (MSCs) [16, 17]. These cells originate from the perivascular niche as pericytes and occur in appreciable numbers in the nucleated cell fraction of human bone marrow concentrate (BMC) [18–20]. Previously, we reported a prospective safety and feasibility study in which there was radiographic improvement in 40% of patients after 12 months and significant improvements in ODI and VAS scores through 24 months [15, 21]. Most intriguing was a correlation between progenitor colony forming units-fibroblast (CFU-F, synonymous with MSCs) and the extent of clinical improvement. In the current study, posterior iliac crest bone marrow aspirate (BMA) was concentrated and reinjected into degenerated intervertebral discs in patients with moderate to severe discogenic low back pain during a single procedure as an alternative to spinal fusion or artificial disc replacement.

Materials and methods

Clinical protocol

This study is a prospective, open-label, non-randomized, single-arm study using the data from four FDA IDE studies as a comparative baseline. The current study and the four comparative IDE studies were conducted with an IRB approved clinical protocol. Inclusion/exclusion criteria were similar in the four studies and the current study. Patients enrolled as subjects in the study (after approved informed consent) presented with symptomatic moderate to severe discogenic low back pain as defined according to the following criteria: centralized chronic low back that increased with activity and lasted at least six months; undergone non-operative management for three months without resolution; shown a change in normal disc morphology as defined by MRI evaluation; have a modified Pfirrmann (MRI) score of 4–7; have a Modic Grade II change or less; disc height loss of <30% compared to an adjacent non-pathologic disc; pre-treatment baseline ODI score of at least 30 on the 100-point scale; and pre-treatment baseline low back pain of at least 40 mm on the 100 mm VAS [22]. An intact annulus was not required to be in the study. Standard exclusion criteria included: an abnormal neurologic exam, symptomatic compressive pathology due to stenosis, a disc herniation causing compressive nerve signs or symptoms, or any spondylolisthesis or spondylolysis. Inclusion/exclusion criteria were similar to all referenced FDA IDE studies reviewed in this study.

All consecutive patients underwent a pre-injection medical history and physical examination including MRI, ODI, and VAS. These ODI and VAS tests were repeated at three, six, 12, 24, and 36 months following the procedure. All patients had a normal neurologic examination of the lower extremities, demonstrated a loss of lumbar range of motion, and had pain to deep palpation over the symptomatic disc(s) with associated muscle spasm. Study patient demographics are listed in Table 1. Thirteen patients underwent an intradiscal injection of autologous BMC at a single symptomatic lumbar disc and 13 subjects had two adjacent symptomatic disc levels injected. Discography was performed in four patients in the one-level group and three patients in the two-level group to ascertain the symptomatic disc. All other patients were injected based on MRI scanning and examination according to inclusion criteria. MRI scans were repeated at 12 months in 20 of 26 patients and assigned a modified Pfirrmann score by a blinded independent reviewer.

Bone marrow collection and processing

BMA (54 ml) was collected over acid citrate dextrose-anticoagulant (ACD-A, 6 ml) from the patient's posterior iliac crest. The procedure was performed with IV sedation consisting of Versed and Fentanyl. Positioning of the Jamshidi needle in the iliac wing was confirmed by fluoroscopy. The local periosteum was anesthetized with 10 ml 1% lidocaine solution at least five minutes prior to aspiration. BMA was collected in a 60 ml syringe in a series of discrete pulls on the plunger (targeting a collection of 5–10 ml per pull) with repositioning of the needle tip between pulls based on the reported enrichment of progenitor cells by Hernigou et al. [20, 23]. The BMA was processed using the ART21 bone marrow concentration system (Celling Biosciences, Austin, TX) to produce BMC cell preparation. Typically, a BMC volume of 7 ml (6 ml for injection and 1 ml for laboratory cell analysis) was drawn from the processed device. A 1 ml sample from each patient's BMC was shipped overnight at 5 °C to a laboratory for cellular analysis assays. Cell analysis included total nucleated cell (TNC) concentration and viability, standard ten day in vitro CFU-F assay at dilutions of 50,000 to 1

Table 1 Patient demographics: demographics of study patients by number of discs (levels) injected, age, gender, BMI, cause of injury, Pfirrmann grade, and BMC characterization

Number of enrolled patients		26
Age range		18–61 years (median 40)
Male:female		11:15
Average BMI		26.6 (range 19–37)
Cause of injury	*Trauma*	12
	Unknown	14
Pre-treatment modified Pfirrmann score (number of discs)	*Grade IV*	3
	Grade V	11
	Grade VI	15
	Grade VII	10
Number of patients with improved Pfirrmann score at 12 months		8 of 20
Average total nucleated cell (TNC) concentration in BMC		121×10^6 per ml
Average CFU-F concentration in BMC		2713 per ml
Average CD34+/lineage– cell concentration in BMC		1.82×10^6 per ml
Patients who received 2nd BMC injection		2
Surgery patients after 24 months		5
Surgery patients after 36 months		6
Surgery patients improved after surgery from pre-injection ODI and VAS		1 of 6

million TNC per well (cultured in 12 well plates at 37 °C with medium containing 10% fetal bovine serum), and osteogenic and chondrogenic differentiation assays to confirm multipotency of MSCs [24]. Flow cytometric analysis was performed on a BD Accuri C6 flow cytometer and included fluorescent antibodies for human CD34 (haematopoietic and endothelial progenitors), CD90, CD105, and a haematopoietic-committed (non-progenitor) lineage panel consisting of CD45, CD3, CD8, and CD10. Candidate MSC populations were considered CD90+/CD105+/lineage– and candidate haematopoietic and endothelial progenitors were considered CD34+/lineage– [19, 25].

Intradiscal injection

With the patient in a prone position, the injection site(s) was treated with local anesthetic (1% buffered lidocaine). BMC was percutaneously injected into the symptomatic disc(s) through a standard posterolateral discogram approach with a two-needle technique. The injection point of the 22-gauge needle was verified with fluoroscopy without use of contrast agent. Approximately 2–3 ml of BMC were used per symptomatic lumbar disc injection. Patients were prescribed pain medicine to be used as needed for three days and put on restricted physical activity for two weeks.

Clinical outcomes determination and statistical analysis

ODI and VAS scores were collected from patients by non-investigator personnel employed by the clinic. Pre-treatment and 12-month MRI were analyzed by a blinded, independent radiologist. Univariable data comparisons were analyzed by two-tailed Student's t-test with a 95% confidence interval ($\alpha = 0.05$, Microsoft Excel). Multivariable data were determined with analysis of variance (ANOVA) using JMP 9 statistical analysis software (SAS Institute, Cary, NC).

Results

Patient reported outcome measures

Patient demographics are reported in Table 1. Baseline average ODI and VAS scores for non-surgery patients were 56.7 (± 3.6 standard error) and 82.1 (± 2.6) respectively. At 3 years, the average ODI score for the 20 patients who had not undergone surgery was 17.5 ± 3.2, while the average VAS score was 21.9 ± 4.4 ($p < 0.001$ for both compared to baseline). These results are illustrated in Fig. 1. The six patients who elected to undergo surgery had baseline average ODI and VAS scores of 56.0 ($p = 0.919$) and 71.4 ($p = 0.098$, with surgery patients reporting 10.7 points lower average baseline VAS than surviving subjects) respectively, not statistically different that patients remaining in the study through 36 months.

Adverse events

Other than progression to surgery, there were no serious adverse events related to the study. Most patients experienced transient pain at the aspiration and injection sites that typically resolved within 48 hours (aspiration site) to seven days

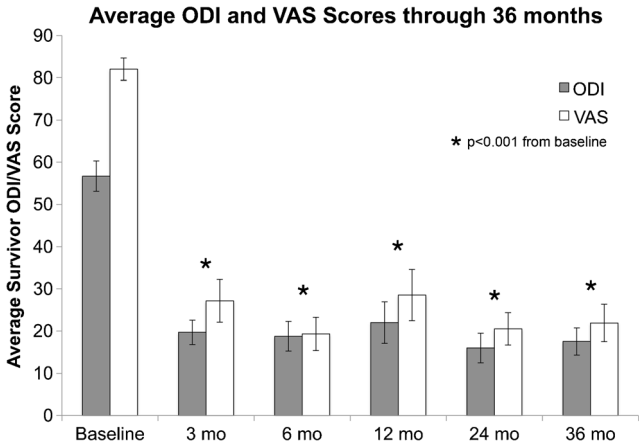

Fig. 1 Average survivor (non-surgery, $n = 20$ at 36 months) patient ODI and VAS scores prior to BMC intradiscal injection (baseline) through 36 months. Error bars represent standard error. All time post-injection scores represented statistically significant differences from pre-treatment pain scores ($P < 0.001$)

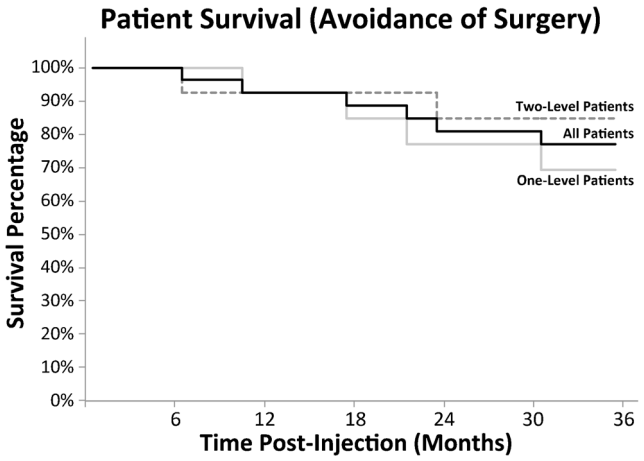

Fig. 2 Kaplan Meier 3-year survival graph of study patients for all 26 enrolled patients (*black*), 13 one-level patients (*solid gray*), and 13 two-level patients (*dashed gray*)

(injection site) following the procedure. No patient reported increases in VAS or ODI upon follow-up examination.

Analytical data and imaging

MRI imaging showed eight out of 20 patients with imaging had at least a one grade increase on the modified Pfirrmann grading scale for disc degeneration at one year. No patients presented a worse MRI score after one year. Patients with higher MSC concentration measured as CFU-F/ml tended to have better outcomes than those with lower concentrations.

Cellular analysis

As previously reported for the study's BMC samples, the average TNC concentration was 130 million per ml, the average mesenchymal (CFU-F) cell concentration was 2702 per ml, and the average haematopoietic-endothelial progenitor (CD34+/lineage–) concentration was 1.66 million per ml.

Progression to surgery, re-injection, and correlations with BMC cellularity

All patients were referred to this study after seeking a surgical consult from the lead author (artificial disc replacement or fusion). After their BMC injection, two patients elected to have a surgical procedure within one year (7 and 11 months), three patients elected to have surgery between one and two years (18, 22, and 24 months), and one patient between two and three years (28 months) for a total of six patients through three years. A Kaplan Meier survival graph is presented in Fig. 2. There were no statistical differences between survivors and surgery dropouts in age, gender, BMI, number of levels injected, or cellularity of BMC. ODI and VAS scores were tracked in relation to mesenchymal (CFU-F) and haematopoietic (CD34+) progenitor cell concentrations (Fig. 3). The most statistically relevant effect was CD34+ cell concentration ($p = 0.14$). Changes in three and six month ODI and six month VAS score were statistically significantly different between surgical and non-surgical subjects ($p < 0.05$).

Discussion

Few treatments for chronic discogenic low back pain have demonstrated long term efficacy. Artificial disc replacements experience wear and their longevity has not been established. Disc degeneration is often observed at levels adjacent to spinal fusion. Non-surgical treatments, including injections tend to have a short-term efficacy. Each therapy has advantages and drawbacks as well as specific populations that respond differently. While it is unlikely the clinical results reported in this study are permanent, the continued success for most of the patients indicates it is durable up to three years post BMC injection with minimal safety concerns. There a slight decrease was observed in ODI and VAS scores from two to three years post procedure. The lumbar disc is the largest avascular structure in humans with little capacity to heal after traumatic injury [26]. Therein lies the hypothesized advantage of biological treatments. They may provide natural healing mechanisms to avascular tissues that might otherwise continue to degenerate. Based on this early evidence, the potential for this treatment to slow down or even temporarily halt the degeneration process is intriguing. No patient was made worse from the bone marrow concentrate injection and there were no serious complications associated with the procedure. This is a good early indicator of the safety of the treatment. A

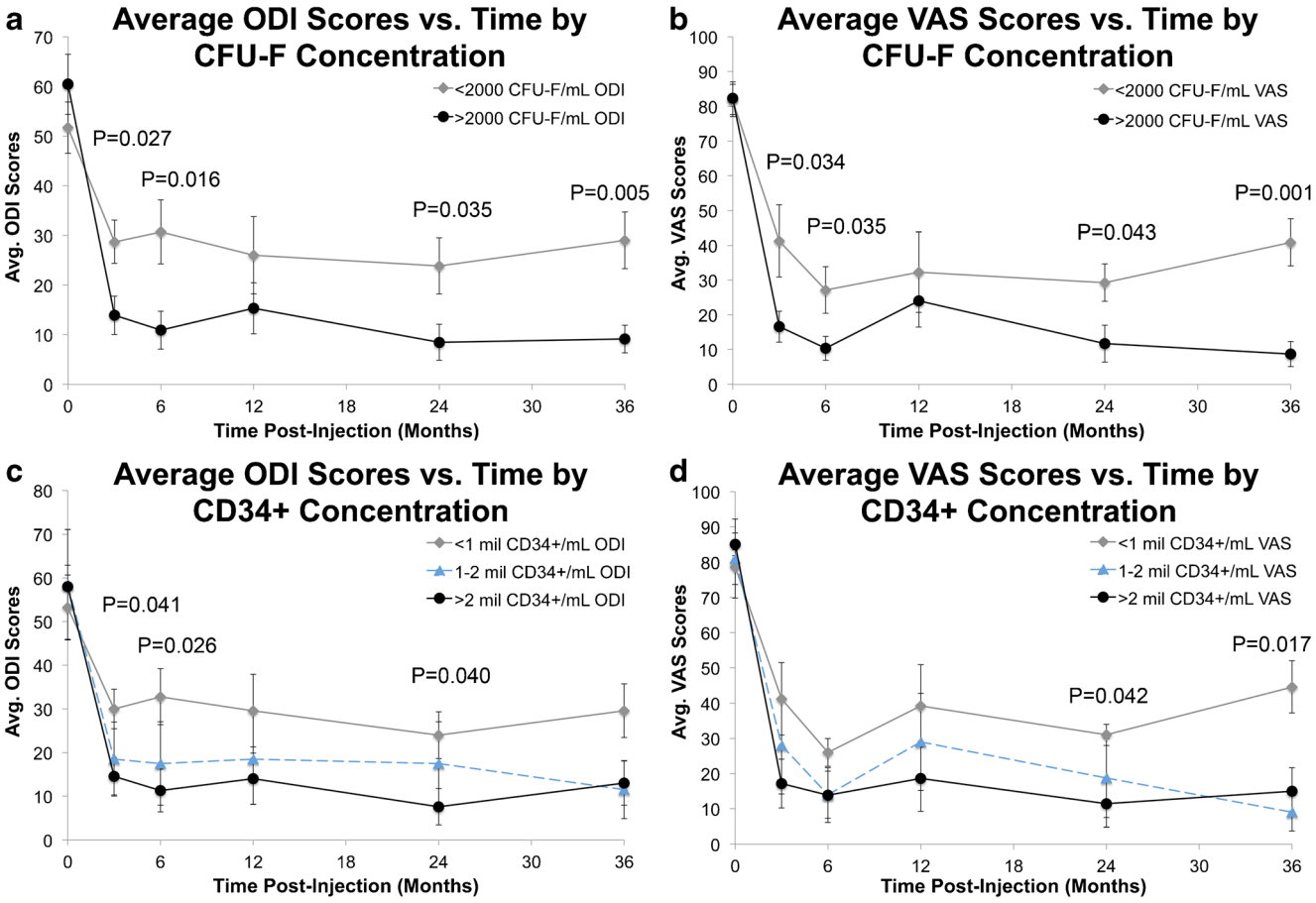

Fig. 3 Average ODI and VAS pain scores of survivor subjects through 36 months based on CFU-F or CD34+ cell concentrations in BMC. **a** ODI by CFU-F, **b** VAS by CFU-F, **c** ODI by CD34+, **d** VAS by CD34+. *P*-values indicate statistically significant differences ($P < 0.05$) between greatest and least cell concentration groups at the various time points

significant contributing factor to the overall safety is that the treatment does not require general anesthesia, but is done with conscious sedation. Unforeseen reactions to general anesthesia are a large source of morbidity and mortality in surgical procedures [27].

The exact cause of discogenic back pain is not well established. It is generally accepted that disc degeneration is a result of a combination of factors including mechanical wear, spinal instability, and genetic predisposition [6, 26, 28]. Surgery in most cases can temporarily address changes from mechanical wear/stress and spinal instability but there are many cases where the loss of motion from spinal fusion contributes to adjacent disc degeneration due to alterations in spine kinematics. Genetic abnormalities are not addressed by surgery, leaving the patient susceptible to continued degenerative changes at other disc levels. While there is no in vivo human evidence of genetic changes in the disc structures from bone marrow concentrate injections, there is significant preclinical evidence that the MSCs contained in bone marrow as well as the other nucleated cells in the prepared concentrate contribute to decreased inflammatory response, improved cell repair, and tissue regrowth [19, 29]. There is also limited evidence from the MRI follow-up in the previously published studies showing an increase in hydration of 40% (8/20) of patients with a follow-up MR image [15, 21]. BMC injection into the disc may provide a long-term advantage over surgery by addressing the mechanical wear and genetic aspects of disc degeneration.

The current authors have reported their minimum one- and two year follow-up studies in peer reviewed journals. This study represents a three year follow-up on 100% of the patients who had not undergone surgery. Three years after enrollment into this study, only six of 26 patients have left the study and undergone surgical treatments. Every patient evaluated in this study was a referral for a surgical consultation to the principal author and met FDA criteria as an appropriate candidate for either artificial disc replacement or fusion with a diagnosis of discogenic back pain [7]. The three year follow-up results of these patients indicates a better clinical result than that reported by Phillips et al., for the non-surgical or surgical treatment of patients with the same diagnosis and also published FDA IDE Data comparing artificial disc replacement with fusion. This indicates a potential advantage of BMC over surgical procedures. The two year follow-up study indicated

Table 2 Comparison of lumbar BMC intradiscal injections to US FDA IDE studies for lumbar spinal fusion and total disc replacement (TDR) surgeries with average 2-year follow-up data and associated factors (7,30). BMC injection 2-year ODI and VAS data includes all patients enrolled at 24 months ($n = 21$)

	BMC injection (current study)		Average of 4 IDE spinal fusion studies (range)		Average of 4 IDE TDR studies (range)	
# of patients	21 of original 26		519		944	
Patient age	38.5		39.9 (18–65)		39.6 (18–70)	
Male:female	8:13		245:274		482:462	
BMI	26.2		27.6		26.4	
Complication rate	0.0%		6.7–7.0%		1.8–2.5%	
Procedure/surgery time	30–45 min		229–272 min		105–160 min	
Length of hospital stay	None		4–5 days		2–4 days	
Procedure/surgery cost	$3–6000		$50–125,000		$35–75,000	
Pain scores	ODI	VAS	ODI	VAS	ODI	VAS
Pre-procedure	56.2	81.5	57.3 (55–65)	75.8 (73–80)	56.5 (53–65)	76.4 (72–80)
3-month	19.9	27.0	31.5 (29–44)	36.8 (27–42)	28.6 (23–38)	32.2 (18–39)
6-month	19.0	18.7	29 (24–44)	29.6 (24–44)	25.2 (20–35)	28.4 (18–38)
12-month	22.3	28.1	26.5 (25–41)	31.6 (25–36)	23.8 (19–34)	29.2 (18–36)
24-month	18.3	22.9	26.2 (19–39)	29.2 (24–38)	24 (19–30)	27.6 (18–32)

five patients had elected to proceed with surgery. Between the two year study and three year study, one additional patient elected to proceed with surgery. Only one of the six patients who elected to have surgery reported any significant improvement from the surgery compared to their pre-injection ODI and VAS scores. This indicates the complexity of treating chronic discogenic back pain with surgical treatment.

The two year follow-up data from four FDA IDE studies were compared to the two year results of this follow-up study (Table 2) [7, 8]. The patient diagnoses were similar in all studies. Inclusion/exclusion criteria were very similar in all studies. All patients had either one or two-level disc procedures. The overall improvement with an artificial disc was a 57% improvement in ODI and 63% improvement in VAS. The overall improvement with a lumbar fusion was 43.3% improvement in ODI and 52.7% improvement in VAS. This compares with a 71% improvement in ODI and 70% improvement in VAS in this BMC injection group (present study). The difference in hospital stay (2.2 to 5 days) in the surgery groups versus one hour in the BMC group is significant. Also very significant is the difference in cost between surgery and the BMC procedure. Other differences include complication rates and re-operations. Not detailed is the significant difference in morbidity and recovery times between all the surgical and the injection groups.

Cellular analysis suggests patients with greater concentrations of progenitor cells (both CFU-F and CD34+/lineage– cell types) in their BMC experienced faster and greater pain reduction. By scatter plot of all patient data, natural subpopulations immerged based on clinical outcomes, namely CFU-F concentrates greater and less than 2000 per ml, and CD34+/lineage– concentrations less 1 million per ml, between 1 and 2 million per ml, and greater than 2 million per ml. It is unlikely that these effects are completely independent, as patients with greater CFU-F concentrations tended to have greater CD34+ concentrations as well. It has been hypothesized that hematopoietic stem cells (a major subset of CD34+) also play an immunomodulatory role similar to MSCs, although any synergistic effect applicable to intradiscal therapy is unknown. This is the first study to link a clinical improvement to CFU-F and CD34+ cell concentrations in BMC.

Limitations of this study as reported in the two year follow-up include the small population (26), the lack of randomization with a control group, and MRIs were only obtained in 20 of 24 surviving patients at the 12-month follow-up. These three year results in 100% of remaining patients indicate that injecting a patient at one or two levels with a diagnosis of chronic discogenic back pain under IV sedation in a 30-minutes procedure with bone marrow concentrate has the potential to provide a non-surgical option for patients with this diagnosis. The morbidity and cost of this percutaneous procedure are substantially less than a surgical option and the clinical results appear to be similar or superior to surgery for chronic discogenic low back pain.

Compliance with ethical standards

Conflict of interest KP has no financial disclosures. RS, TS, and MM are employees of Celling Biosciences, a medical device manufacturer who provided devices for bone marrow concentration in the current study.

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Informed consent All enrolled subjected provided informed consent according to written consent form approved by Institutional Review Board. The clinical study was approved by Western Institutional Review Board protocol number 20120085.

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