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CLINICAL TRIAL REPORT

Supplemental Nucleus Pulposus Allograft in Patients with Lumbar Discogenic Pain: Evaluation of Clinical Outcomes and Quality of Life in Medicare Beneficiaries

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Background: The healthy nucleus pulposus (NP) of the intervertebral disc is normally replete with proteoglycans and highly hydrated. With degeneration, the disc loses its capacity to bind water, substantially reducing its ability to cushion physiologic loads. Supplementation of degenerated NP with a commercially available NP allograft represents a promising approach to ameliorating lumbar discogenic pain.

Methods: This was a prospective, single arm clinical study involving 21 patients at 5 US sites. The magnitude of improvement in back pain severity, back disability and quality of life was evaluated in Medicare-age (≥65 years) patients with chronic axial low back pain treated with intradiscally delivered NP allograft at up to three lumbar vertebral levels (L1-S1). Followup was at 1, 3 and 6 months. Back pain was determined using an 11-point numeric rating scale (NRS), back function by Oswestry disability index (ODI) and quality of life using the PROMIS-29 questionnaire.

Results: There was a 60% reduction in average back pain scores between baseline and 6 months; the difference (4.0, 95% CI [2.9, 5.2]) was statistically significant ($p < 0.001$). 82% and 71% of participants achieved ≥30% and ≥50% NRS improvement, respectively, at 6 months, and 65% of participants reported a final NRS score ≤3. The 6-month improvement in mean ODI scores was 50% with an average difference of 22.8 (95% CI [14, 31]) ($p < 0.001$). 68% and 51% realized ≥30% and ≥50% ODI improvements, respectively, at 6 months. All PROMIS-29 domains showed improvements toward the normative mean value of 50 by 6 months. No adverse events related to the NP allograft were reported.

Conclusion: These findings show clinically significant pain palliation, functional improvement and quality of life enhancement in older adults following supplementation of the degenerated disc with NP allograft.

Keywords: discogenic, low back pain, nucleus pulposus, allograft, medicare, PROMIS-29

Introduction

The intervertebral disc is the initial structure in the lumbar vertebral motion segment to demonstrate morphological changes indicative of spinal degeneration.[1] Invariably, loss of disc height precipitates a cascade of further degenerative structural changes that involve the facet joints as well as the neural foramina and lateral recesses.[2,3] This process commences in early adulthood with both biochemical and anatomical degenerative changes evident on magnetic resonance imaging (MRI) in patients with chronic axial low back pain.[4–7] In the elderly, the prevalence of imaging evidence of intervertebral disc degeneration exceeds 90%.[3,8–10]

Within the intervertebral disc, the nucleus pulposus (NP) sustains the first characteristics of degeneration.[11,12] Although a healthy NP is replete with proteoglycans and remains highly hydrated, with degeneration the intervertebral

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disc loses its capacity to bind water under compression, substantially reducing its ability to cushion physiologic loads.[13] Consequently, there has been an extensive research and development effort with the objective to evaluate and validate minimally invasive intradiscal therapies to restore the integrity of the intervertebral disc and ameliorate lumbar discogenic pain.[14]

Direct supplementation of degenerated NP tissue with a commercially available NP allograft represents a promising approach to managing painful intervertebral discs.[15] Since the proteoglycans within the allograft NP tissue effectively bind water, the strategy is to restore the mechanical cushioning properties of the disc through implantation.[16,17] Processed with minimal manipulation, supplementation of tissue lost to degenerative disc disease with intradiscally delivered NP allograft is a straightforward homologous replacement procedure intended to improve pain, function and quality of life.

Given the almost universal prevalence of intervertebral disc degeneration in the elderly, the current study was undertaken to evaluate the preliminary safety and effectiveness of supplementing depleted NP tissue due to pathological degradation of the disc with NP allograft in patients ≥65 years of age diagnosed with chronic lumbar discogenic pain.

Methods

This was a prospective, single arm, multicenter clinical study at 5 sites in the US. We determined the magnitude of improvement in lumbar discogenic pain severity, back disability and quality of life in Medicare-age patients with chronic axial low back pain. Treatment consisted of NP allograft tissue delivered intradiscally at up to three lumbar vertebral levels (L1-S1). Intradiscal NP allograft was the only product administered. This study was conducted in compliance with the Declaration of Helsinki and prospectively registered at ClinicalTrials.gov on June 9, 2022 (NCT05412277). All patients provided informed consent. The study was reviewed and approved on June 16, 2022 by an independent institutional review board (IRB), Sterling IRB (Atlanta, GA, USA) and the first subject was enrolled on October 17, 2022.

Physical examination was undertaken to verify lumbar discogenic pain using established signs and symptoms.[18,19] All study participants demonstrated axial midline low back pain with or without non-radicular/non-sciatic referred leg pain as the primary symptom. There was absence of lower extremity motor, sensory, or reflex changes. Additional inclusion criteria noted at physical examination included intolerance to prolonged sitting as well as pain provoked with forward flexion and the sustained hip flexion maneuver.[20] Eligible subjects included patients 65 years of age or older, with a body mass index (BMI) ≤35, with radiographic evidence of moderate to severe degeneration of up to 3 intervertebral discs from L1 to S1 on magnetic resonance imaging (MRI), with associated chronic lumbar discogenic pain for ≥6 months following failed conservative care of at least two modalities, modified Pfirrmann Grade 3–7, no Modic changes or if changes ≤2. Study participants also had an Oswestry Disability Index (ODI) score of ≥21 and ≤80 points and low back pain numeric rating scale (NRS) score ≥5 on an 11-point scale. Discography was not required to confirm eligibility.

Patients exhibiting signs and/or symptoms of neurocompressive, facetogenic, vertebrogenic, sacroiliac or radicular sources of back pain were excluded. Additional exclusion criteria included index level spinal conditions such as disc herniation/protrusion, spondylolisthesis, and inflammatory spinal disorders as well as previous lumbar spine fusion surgery or disc arthroplasty at the treated level(s), lumbar epidural steroid injections within 4 weeks or radiofrequency ablation within 8 weeks, prior stem cell therapy for the intervertebral disc(s), traumatic neurological disorders, 3 or more Waddell's signs, and spinal fractures.

A single dose of VIA Disc NP (VIVEX Biologics, Inc., Miami, FL, USA) was delivered intradiscally to each affected intervertebral disc(s).[15] This product is commercially available and consists of dehydrated, micronized allograft tissue delivered as a 100 mg (± 10%) aliquot. At the time of the procedure, the product is rehydrated with 2 mL of sterile saline for delivery into the target intervertebral disc(s) through a 20G cannula. NP allograft particulate like native NP contains glycosaminoglycans (GAGs), suggesting a proteoglycan-based mechanism by which water absorption occurs and mechanical cushioning is supported. NP allograft tissue particulate from 40 donors was analyzed for its GAG content as well as water absorption capacity (WAC). The average GAG content in disc tissue from all donors was 666.1 (± 156.9) ug/mg tissue particulate. The average WAC in NP tissue from all donors was 608.4 (± 113.1) %.

Moderate conscious sedation is used during the procedure as well as a local anesthetic at the cannula entry site. Correct placement of a small gauge delivery cannula is confirmed using fluoroscopic guidance. Disc access with the delivery cannula is achieved via a posterolateral approach through Kambin's triangle with NP allograft injected according

to the product Instructions for Use (IFU).[15] Following the procedure, patients can return home the same day and can resume normal activities the following day.

Post procedure clinical followup was undertaken at 1, 3 and 6 months to evaluate patient reported outcomes and the occurrence of adverse events. Back pain severity was measured using the 11-point NRS, back function by ODI and quality of life using the PROMIS-29 questionnaire instrument which measures common patient symptoms and disease impacts across a range of physical, emotional, and social health domains.[21] The PROMIS-29 instrument is a 29-item fixed short form profile that covers 8 areas (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles, pain interference, and cognitive function).

At baseline and at each followup interval, all patient reported outcomes are presented as means (± 95% CIs) with the overall improvement determined using repeated measures analysis of variance (ANOVA). The paired *t*-test, 2-tailed was used to confirm the difference between baseline values and the 6-month endpoint. Responder rates at 6 months for NRS and ODI were calculated based on a minimal clinically important difference (MCID) of ≥30% and substantial clinical benefit (SCB) of ≥50% improvement compared to baseline values.[22–24] Additionally, the Wilcoxon signed rank test was used to compare ODI values at baseline and 6 months categorized by functional impairment severity as minimal (0–20), moderate (21–40), severe (41–60), and crippled (61–80). The 6-month responder rate for NRS patient acceptable symptom state (PASS) score was also computed with a success threshold set at ≤3.[25] The PROMIS-29 scores were normalized to a standard population distribution with a mean of 50 and a standard deviation of 10 (i.e, T-score) for each of the 8 domains. Higher scores represent more of the domain being measured, eg, higher scores in physical function indicate better health, while higher scores in anxiety or depression indicate worse mental health. We also computed the PROMIS-29 Preference Score which summarizes multiple domains on a metric from 0 to 1 and the Global Pain Intensity Scale score which measures overall pain intensity.[26] The frequency and severity of adverse events were captured at each post procedure followup interval.

Results

A total of 29 subjects were screened, 21 of which met all inclusion and exclusion criteria and were enrolled in the study, underwent the intradiscal procedure, and have been included in the analyses (Figure 1). The average age of this study group was 69.9 ± 4.1 years, and included 9 (43%) female patients. Four subjects were treated at 1 level (19%), eleven at 2 levels (52%), and six at 3 levels (29%). One subject demonstrated a highest modified Pfirrmann grade 4 (5%), four with grade 5 (19%), six with grade 6 (28%), and ten with grade 7 (48%).

There was a reduction of approximately 60% (95% CI [43%, 78%]) in average back pain severity scores from 6.6 (95% CI [6.1, 7.1]) at baseline to 2.6 (95% CI [1.5, 3.7]) at 6 months post procedure, and the difference (4.0, 95% CI [2.9, 5.2]) was statistically significant ($p < 0.001$) (Figure 2). The MCID of ≥30% improvement over baseline was achieved in 82% (17 of 21) of study participants at 6 months, with 71% (15 of 21) realizing a SCB of 50% improvement over baseline. Approximately 65% (14 of 21) of participants reported a final pain NRS score ≤3 at the 6-month followup visit.

Comparable symptomatic improvements in back function were also realized post procedure with an approximate 50% (95% CI [34%, 67%]) reduction in average ODI scores from 44.7 (95% CI [38, 51]) at baseline to 21.9 (95% CI [13, 31]) at 6 months, and the difference (22.8, 95% CI [14, 31]) was statistically significant ($p < 0.001$) (Figure 3). Approximately 68% (14 of 21) and 51% (11 of 21) of participants achieved the MCID and SCB, respectively, for ODI at 6 months. Figure 4 provides the distributions of ODI functional impairment categories at baseline and 6 months. At baseline, 53% of study participants reported an ODI value reflecting a severe or crippled degree of back impairment. This percentage was reduced to approximately 11% at the 6-month followup visit, with almost 53% of patients reporting minimal disability at this interval, and difference in these distributions was statistically significant ($p < 0.001$).

Table 1 provides the PROMIS-29 mean values (95% CIs) at baseline, 3, and 6 months for the eight quality of life domains as well as the preference and global pain intensity scale scores. All domains showed significant improvements in the direction of the normative mean value of 50 by 6 months except for the anxiety subdomain. The average preference scores more than doubled between baseline (0.24, 95% CI [0.17, 0.30]) and 6 months (0.51, 95% CI [0.39, 0.62]) and the difference was statistically significant (0.25, 95% CI [0.14, 0.37]). The global pain intensity scale scores improved by an

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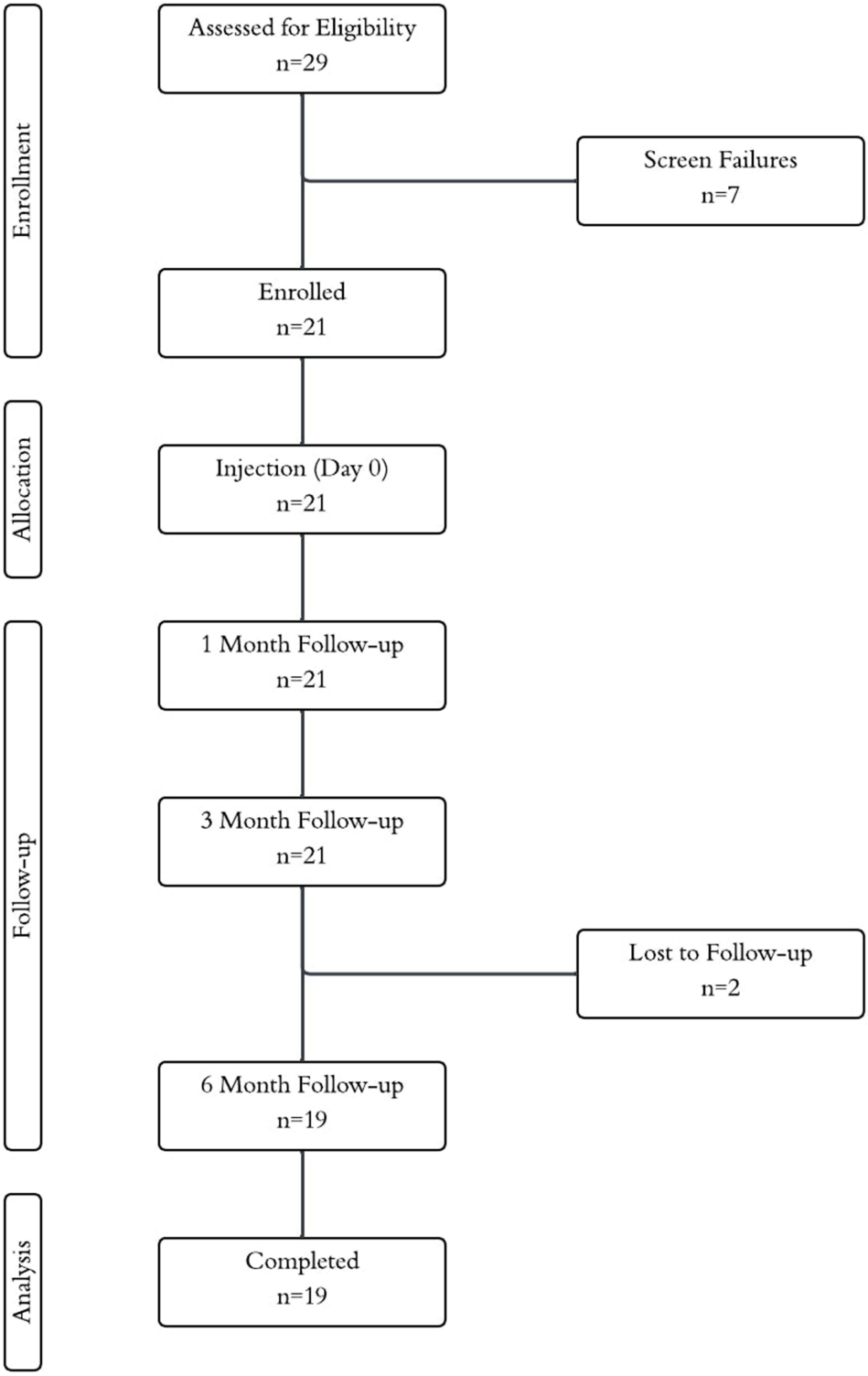

Figure 1 Study flow diagram.

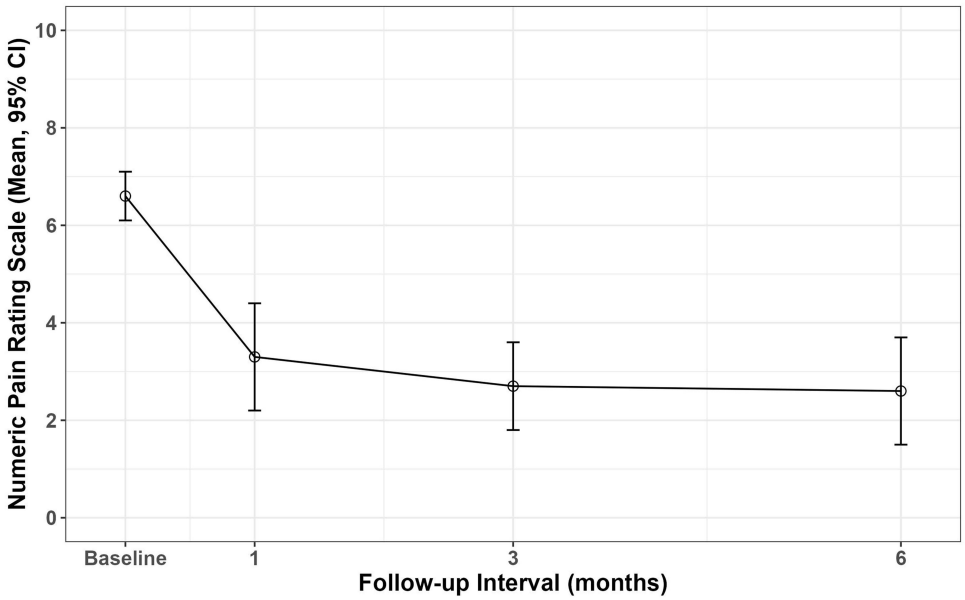

Figure 2 Line graph showing an average overall longitudinal improvement of 60% in back pain severity scores through 6 months of post procedure followup ($p < 0.001$). Mean NRS values are 6.6 (baseline), 3.3 (1 month), 2.7 (3 months), and 2.6 (6 months). N = 21 at baseline and all followup intervals.

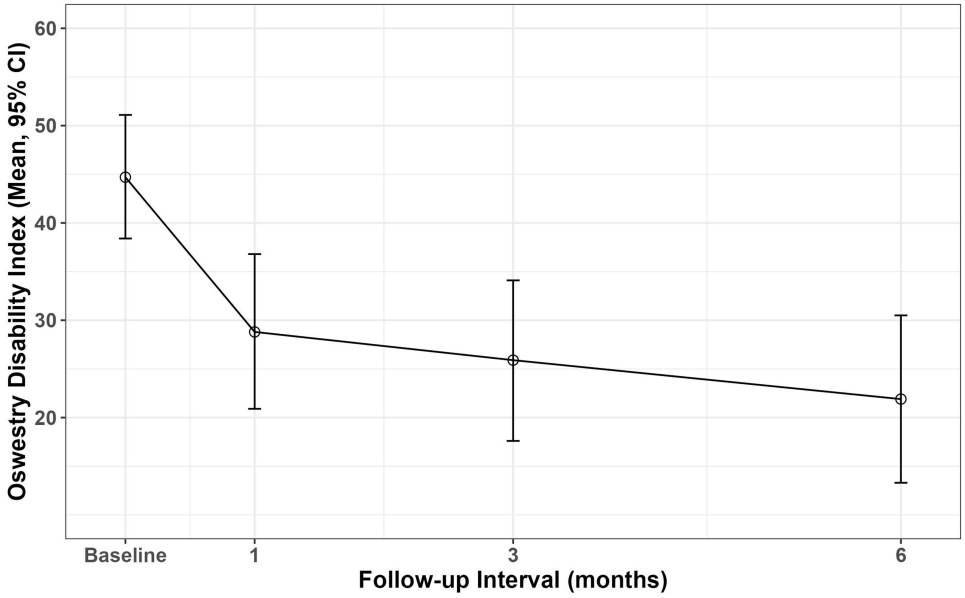

Figure 3 Line graph showing an average overall longitudinal improvement of 50% in back function scores through 6 months of post procedure followup ($p < 0.001$). Mean ODI values are 44.7 (baseline), 28.8 (1 month), 25.9 (3 months), and 21.9 (6 months). N = 21 at baseline and all followup intervals.

average 4.1 points (95% CI [3.1, 5.1]) between baseline (6.6, 95% CI [6.0, 7.1]) and 6 months (2.5, 95% CI [1.5, 3.5]) post procedure. There was no association between number of treated levels and any of the foregoing clinical outcomes.

There were 7 adverse events, two of which were categorized as serious. One patient experienced a transient ischemic attack and the other contracted COVID-19, and both required hospitalization. Neither serious adverse event was related to either the NP allograft or the intradiscal procedure. No adverse events were considered related to NP allograft and only one was considered probably related to the intradiscal procedure, which was mild in severity and resolved without sequelae.

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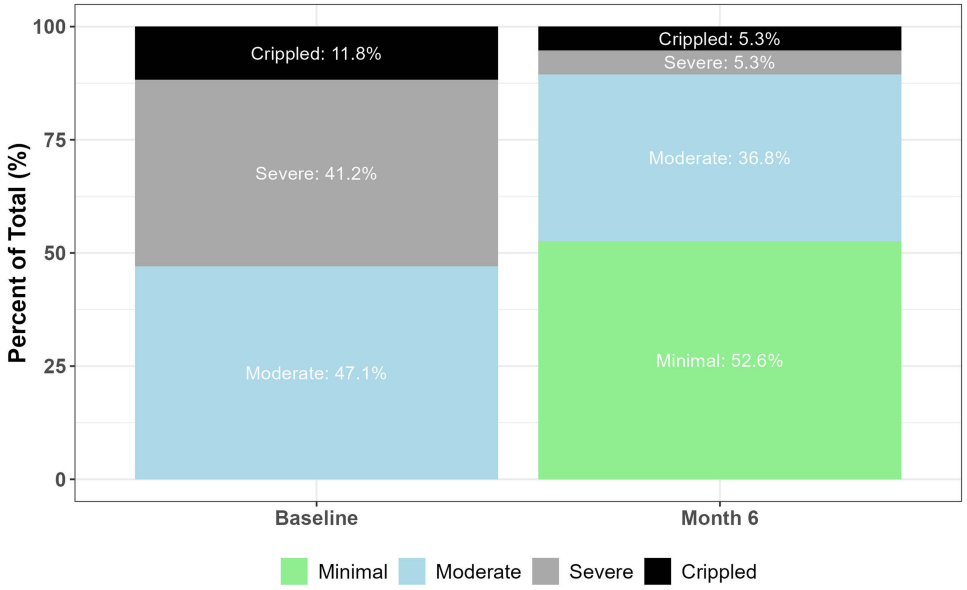

Figure 4 Comparative distributions of ODI functional impairment categories at baseline and 6 months post procedure. The difference in these distributions was statistically significant ($p < 0.001$).

Discussion

This is the first study to evaluate the safety and effectiveness of NP allograft in a Medicare-aged population of subjects diagnosed with chronic lumbar discogenic pain associated with degenerative disc disease. Previous investigations of NP allograft supplementation and other intradiscal therapies have generally focused on younger age populations in an effort

Table 1 PROMIS-29 Quality of Life, Preference and Global Pain Intensity Scale Scores at Baseline, 3 and 6 months.

	Baseline	3 Months	Change at 3 Months	6 Months	Change at 6 Months
n	21	21	21	19	19
Physical Function					
Mean (SD)	37.78 (4.81)	43.61 (7.80)	5.83 (7.24)	44.28 (6.59)	5.94 (6.58)
95% CI	(35.59, 39.97)	(40.06, 47.16)	(2.53, 9.12)	(41.10, 47.45)	(2.76, 9.11)
Anxiety					
Mean (SD)	49.78 (9.25)	45.87 (8.76)	−3.91 (8.31)	44.73 (7.83)	−4.03 (8.53)
95% CI	(45.57, 53.99)	(41.88, 49.85)	(−7.69, −0.13)	(40.95, 48.50)	(−8.14, 0.08)
Depression					
Mean (SD)	48.74 (9.01)	45.48 (7.46)	−3.27 (6.07)	44.21 (6.08)	−3.86 (5.79)
95% CI	(44.64, 52.84)	(42.08, 48.87)	(−6.03, −0.50)	(41.28, 47.14)	(−6.65, −1.07)
Fatigue					
Mean (SD)	57.20 (8.31)	48.44 (7.84)	−8.76 (7.59)	44.73 (8.49)	−11.2 (9.62)
95% CI	(53.41, 60.98)	(44.87, 52.01)	(−12.2, −5.30)	(40.64, 48.83)	(−15.8, −6.56)

(*Continued*)

Table 1 (Continued).

	Baseline	3 Months	Change at 3 Months	6 Months	Change at 6 Months
Sleep Disturbance					
Mean (SD)	39.61 (9.14)	36.40 (7.48)	−3.20 (6.12)	34.85 (5.89)	−3.99 (5.83)
95% CI	(35.45, 43.77)	(33.00, 39.81)	(−5.99, −0.42)	(32.01, 37.69)	(−6.81, −1.18)
Social Role					
Mean (SD)	41.61 (7.55)	50.03 (10.20)	8.42 (9.53)	52.59 (10.64)	9.93 (9.28)
95% CI	(38.17, 45.05)	(45.39, 54.68)	(4.09, 12.76)	(47.47, 57.72)	(5.46, 14.40)
Pain Interference					
Mean (SD)	65.78 (6.15)	56.00 (9.32)	−9.78 (8.65)	53.50 (9.47)	−11.2 (9.35)
95% CI	(62.98, 68.58)	(51.75, 60.24)	(−13.7, −5.84)	(48.94, 58.06)	(−15.8, −6.73)
Cognitive Function					
Mean (SD)	48.34 (8.92)	52.90 (9.76)	4.55 (12.10)	54.19 (10.04)	5.74 (15.44)
95% CI	(44.28, 52.41)	(48.45, 57.34)	(−0.96, 10.06)	(49.36, 59.03)	(−1.70, 13.19)
Preference Score					
Mean (SD)	0.24 (0.14)	0.47 (0.26)	0.23 (0.21)	0.51 (0.23)	0.25 (0.24)
95% CI	(0.17, 0.30)	(0.35, 0.59)	(0.14, 0.33)	(0.39, 0.62)	(0.14, 0.37)
Global Pain Intensity Scale					
Mean (SD)	6.57 (1.21)	3.29 (2.15)	−3.29 (2.15)	2.53 (2.06)	−4.11 (2.13)
95% CI	(6.02, 7.12)	(2.31, 4.26)	(−4.26, −2.31)	(1.53, 3.52)	(−5.13, −3.08)

to address the earliest manifestations of intervertebral disc degeneration.[14,15] In contrast, the current study included an age range of 65 to 76 years where nearly 50% of subjects demonstrated modified Pfirrmann grade 7 representing a 30% to 60% reduction in disc height.[27]

Using a single intradiscal administration of allogeneic NP tissue, we found that approximately 82% of subjects experienced clinically significant lumbar discogenic pain relief at 6 months after treatment, with almost 65% of participants enjoying almost complete pain relief with a 6-month pain severity score ≤3.[28] The ≤3 threshold represents the patient acceptable symptom state or PASS which is an important clinical metric for differentiating whether a patient truly feels well as opposed to simply feeling better.[29,30] We observed comparable improvements in back function as well with more than one-half of participants having a 6-month ODI score reflecting minimal impairment.

This is also the first study to report quality of life scores using the PROMIS-29 questionnaire instrument in subjects with chronic lumbar discogenic pain receiving NP allograft supplementation. There was uniform improvement in all eight quality of life domains as well as the preference and global pain intensity scale scores in this study group. For example, the baseline average physical function subdomain value (37.8) was more than a standard deviation (ie, 10) below the population norm value of 50 prior to intradiscal administration of NP allograft. By 6 months, this subdomain improved to within almost a 0.50 standard deviation (44.3) of the population norm.

These clinical findings complement recently published results using the same NP allograft product in a younger population with durable improvements in back pain and function through 2 years of followup.[31]

Degeneration of the intervertebral disc is recognized as a significant source of chronic axial low back pain.[32] The recent issuance of universal diagnostic coding (ICD-10-CM) enumerating the specific diagnostic characteristics of

lumbar discogenic pain associated with degenerative disc disease has had broad implications for spine care.[18,33] In fact, there are numerous minimally invasive intradiscal therapies being developed and evaluated for the management of lumbar discogenic pain.[14,34] Presented here, NP allograft used as a supplemental implant offers a minimally manipulated, off-the-shelf product that provides a nonsurgical option for older adults that does not alter the normal anatomy of the spine.

This pilot study has several limitations that include a small sample of subjects, absence of a concurrent active or placebo control group and lack of followup imaging evidence of potential structural changes within the treated intervertebral disc. These issues limit the generalizability of the current clinical findings and should be addressed in future investigations.

Conclusion

Our more complete understanding of the role of the intervertebral disc in pain generation has spurred renewed interest in this structure as a target for minimally invasive intradiscal interventions aimed at ameliorating lumbar discogenic pain.[14] These approaches and procedures represent an enormous opportunity to improve spine care and enhance quality of life in elderly patients suffering with discogenic back pain. The results of this study provide evidence that intradiscal supplementation of the degenerated intervertebral disc with NP allograft is associated with clinically significant pain palliation, functional improvement and quality of life enhancement. We encourage further research in this patient population to ascertain whether clinical adoption of this procedure provides sustained improvements in activities of daily living for elderly individuals experiencing chronic lumbar discogenic pain.

Data Sharing Statement

Requests for data sharing can be made by contacting the corresponding author. Individual participant data that underlie the results reported in this article will be made available (after deidentification) from 9 to 36 months after article publication. Data sharing will be limited to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose.

Institutional Review Board Statement

This study was conducted according to the ethical principles of the 1964 Declaration of Helsinki and approved by Sterling IRB (Atlanta, GA, USA) on June 16, 2022. Permission was granted from the 5 clinical sites for participation/access to data during the course of the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

JB is an independent advisor to Vivex Biologics and was remunerated for assistance in manuscript development. NA reports grants from Vivex, during the conduct of the study; personal fees from Vivex, outside the submitted work. TM reports personal fees from Medtronic, personal fees from Boston Scientific, personal fees from Vivex, personal fees from SPR Therapeutics, outside the submitted work. JT reports grants, personal fees from Vivex, during the conduct of the study; personal fees from Medtronic, personal fees from Abbott, personal fees from Nevro, grants, personal fees from Saluda, grants, personal fees from Curonix, grants, personal fees from Mainstay, personal fees from Vertos, personal fees

from Stryker, outside the submitted work. CG reports personal fees, research funding from SPR Therapeutics, personal fees from Saluda Medical, personal fees, research funding from Nalu Medical, personal fees from PainTeq, research funding from Shiratronics, outside the submitted work. The authors report no other conflicts of interest.

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