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Clinical Study

A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain

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Abstract

BACKGROUND CONTEXT: Current literature suggests that degenerated or damaged vertebral endplates are a significant cause of chronic low back pain (LBP) that is not adequately addressed by standard care. Prior 2-year data from the treatment arm of a sham-controlled randomized controlled trial (RCT) showed maintenance of clinical improvements at 2 years following radiofrequency (RF) ablation of the basivertebral nerve (BVN).

Research Oversight & Ethics: This research was conducted under the oversight of the Western Institutional Review Board, Advarra IRB and the investigational site's local IRB. Informed consent was obtained for participants in this study. This research was conducted in accordance with the Helsinki Declaration.

FDA device/drug status: Approved (Intracept).

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PURPOSE: The purpose of this RCT was to compare the effectiveness of intraosseous RF ablation of the BVN to standard care for the treatment of chronic LBP in a specific subgroup of patients suspected to have vertebrogenic related symptomatology.
STUDY DESIGN/SETTING: A prospective, parallel, open label RCT was conducted at 20 U.S. sites.
PATIENT SAMPLE: A total of 140 patients with chronic LBP of at least 6 months duration, with Modic Type 1 or 2 vertebral endplate changes between L3 and S1, were randomized 1:1 to undergo either RF ablation of the BVN or continue standard care.
OUTCOME MEASURES: Oswestry Disability Index (ODI) was collected at baseline, 3, 6, 9, and 12-months postprocedure. Secondary outcome measures included a 10-point Visual Analog Scale (VAS) for LBP, ODI and VAS responder rates, SF-36, and EQ-5D-5L. The primary endpoint was a between-arm comparison of the mean change in ODI from baseline to 3 months post-treatment.
METHODS: Patients were randomized 1:1 to receive RF ablation or to continue standard care. Self-reported patient outcomes were collected using validated questionnaires at each study visit. An interim analysis to assess for superiority was prespecified and overseen by an independent data management committee when a minimum of 60% of patients had completed their 3-month primary endpoint visit.
RESULTS: The interim analysis showed clear statistical superiority ($p<.001$) for all primary and secondary patient-reported outcome measures in the RF ablation arm compared with the standard care arm. This resulted in a data management committee recommendation to halt enrollment in the study and offer early cross-over to the control arm. These results are comprised of the outcomes of the 104 patients included in the intent-to-treat analysis of the 3-month primary endpoint, which included 51 patients in the RF ablation arm and 53 patients in the standard care arm. Baseline ODI was 46.1, VAS was 6.67, and mean age was 50 years. The percentage of patients with LBP symptoms ≥5 years was 67.3%. Comparing the RF ablation arm to the standard care arm, the mean changes in ODI at 3 months were −25.3 points versus −4.4 points, respectively, resulting in an adjusted difference of 20.9 points ($p<.001$). Mean changes in VAS were −3.46 versus −1.02, respectively, an adjusted difference of 2.44 cm ($p<.001$). In the RF ablation arm, 74.5% of patients achieved a ≥10-point improvement in ODI, compared with 32.7% in the standard care arm ($p<0.001$).
CONCLUSIONS: Minimally invasive RF ablation of the BVN led to significant improvement of pain and function at 3-months in patients with chronic vertebrogenic related LBP. © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Keywords: Basivertebral nerve; Chronic low back pain; Degenerative disc disease; Endplate degeneration; Minimally invasive surgery; Modic; Radiofrequency ablation; Randomized controlled trial; Vertebrogenic

Introduction

Chronic low back pain (CLBP) affects 10%–13% of the adult U.S. population, or more than 30 million people [1,2]. Often, a specific diagnosis is lacking, making it difficult to establish validated care pathways [3,4]. This results in over- or undertreatment, suboptimal outcomes, and high costs. Furthermore, clinical guidelines and payer policies governing nonoperative and surgical treatments for CLBP are inconsistent and have a high degree of heterogeneity [5].

Although the diagnosis of vertebrogenic pain is a relatively new clinical concept, there is a substantial body of basic science evidence supporting the vertebral endplates as a significant source of LBP [6–11]. Immunohistochemical studies have demonstrated nociceptors at the endplates that trace back to the basivertebral nerve (BVN), a branch of the sinuvertebral nerve that was first described by Antonacci et al. in 1998 [12]. The endplates' dual role of nutritional support for the disc and structural support for the spine are at odds, making them vulnerable to damage. Endplate damage can lead to cellular communication between the immunologically privileged disc nucleus and vertebral bone marrow, triggering chronic inflammation, a process that is visible as Modic changes on magnetic resonance imaging (MRI) [9]. This leads to endplate nerve proliferation that, in the presence of chemical sensitization and mechanical stimulation, can result in pain signals transmitted to the central nervous system by the BVN that are perceived as LBP [6]. These findings led to interest in utilizing therapeutic radiofrequency (RF) ablation of the BVN in a specific subgroup of the chronic LBP population suspected of having vertebrogenic pain.

Following a pilot study [13], a randomized, double-blind, sham-controlled trial of 225 patients demonstrated the efficacy of intraosseous RF ablation of the BVN to treat chronic LBP in patients with Modic type 1 or 2 changes of the vertebral endplates [14]. A follow-up study of the treatment arm of the sham-controlled trial demonstrated durability of those results at 24 months [15]. Based on these findings, a new study was designed and undertaken to evaluate the clinical effectiveness of BVN RF ablation compared to standard care of chronic LBP.

Methods

Trial design

The INTRACEPT trial reported here (registered on ClinicalTrials.gov as NCT03246061) is a prospective, parallel, randomized, controlled, open label, multicenter clinical trial of 140 patients with suspected vertebrogenic chronic low back pain randomized to either RF Ablation of the BVN or continuation of standard care. These study subjects were consecutively recruited at 20 investigative sites in the U.S. from September 2017 to January 2019. Since an earlier and separate sham-controlled trial that ended recruitment in 2014 (registered with ClinicalTrials.gov as NCT01446419) revealed that 3-month treatment outcomes were maintained at 2 years [14,15], the primary endpoint for this new trial was set at the 3-month follow-up. In addition, a prespecified interim analysis for superiority assessment was conducted (per protocol) when 60% of randomized subjects completed 3-month follow-up. An independent Data Management Committee (DMC) oversaw the interim analysis and study decisions. This is a report on the prespecified interim analysis at the 3-month primary endpoint.

The INTRACEPT trial was sponsored by Relievant Medsystems, Inc. (Minneapolis, MN, USA). The study was HIPAA compliant and conducted under Institutional Board Review approval and participant informed consent was obtained. Enrolled patients were assigned a unique participant ID number, and all submitted patient information was deidentified. Data submitted by the study sites was source-verified to the medical record and patient-completed questionnaires by study monitors. A third-party statistician (QST Consultations, Grand Rapids, MI, USA) prepared the computer-generated randomization scheme using permuted blocks of four or six and stratified by study site.

Participants

Eligibility was adjudicated by an independent medical monitor based on each patient's medical, clinical, and radiographic presentation. The primary inclusion criteria included skeletally mature patients with ≥6 months of CLBP who had not responded to at least 6 months of conservative care and had Type 1 or Type 2 Modic changes on an MRI at one or more vertebral bodies from L3 through S1. Primary exclusion criteria included radicular pain, symptomatic spinal stenosis, disc protrusion >5 mm, spondylolisthesis >2 mm at any level, or Beck Depression Inventory of greater than 24. See Table 1 for a complete listing of inclusion and exclusion criteria for this study.

Upon confirmation of eligibility, baseline measurements were collected and entered by the study site research personnel into the online clinical database (iMedNet, Mednet Solutions, Minneapolis, MN, USA). An electronic randomization assignment was provided by the clinical database if the minimum thresholds for ODI (>30 points) and VAS (>4 cm) were met. Patients were electronically randomized 1:1 to either RF ablation treatment or standard care.

Table 1
Listing of the inclusion and exclusion criteria for the study

Inclusion criteria	Exclusion criteria

• Skeletally mature patients with chronic (≥6 months) isolated lumbar back pain, who had not responded to at least 6 months of nonoperative management.
• Type 1 or Type 2 Modic changes at one or more vertebral body for levels L3–S1.
• Minimum ODI of 30 points (100-point scale).
• Minimum VAS of 4 cm (10 cm scale).
• Ability to provide informed consent, read and complete questionnaires.
	• MRI evidence of Modic at levels other than L3–S1.
	• Radicular pain (defined as nerve pain following a dermatomal distribution and that correlates with nerve compression in imaging).
	• Previous lumbar spine surgery (discectomy/laminectomy allowed if >6 months before baseline and radicular pain resolved).
	• Symptomatic spinal stenosis (defined as the presence of neurogenic claudication and confirmed by imaging).
	• Metabolic bone disease, spine fragility fracture history, or trauma/compression fracture, or spinal cancer.
	• Spine infection, active systemic infection, bleeding diathesis.
	• Radiographic evidence of other pain etiology
	  • Disc extrusion or protrusion >5 mm.
	  • Spondylolisthesis > 2 mm at any level
	  • Spondylolysis at any level.
	  • Facet arthrosis / effusion correlated with facet-mediated LBP.
	• Beck Depression Inventory >24 or 3 or > Waddell's signs.
	• Compensated injury or litigation.
	• Currently taking extended release narcotics with addiction behaviors.
	• BMI >40.
	• Bedbound or neurological condition that prevents early mobility or any medical condition that impairs follow up.
	• Contraindication to MRI, allergies to components of the device, or active implantable devices, pregnant or lactating.

ODI, Oswestry Disability Index; VAS, Visual Analog Scale; MRI, magnetic resonance scale; BMI, body mass index.

Study interventions

Patients in the treatment arm received intraosseous RF ablation of the BVN using a unilateral transpedicular delivery system (Intracept System, Relievant Medsystems, Minneapolis, MN, USA). Treatment of up to four vertebrae in nonconsecutive levels from L3 to S1 was allowed. The procedure was performed under image guidance with moderate conscious sedation or general anesthesia, per investigator discretion, in an outpatient setting. The electrode was advanced to the targeted location proximal to the terminus of the BVN, approximately 30%–50% across the sagittal vertebral body width (Fig. 1). Following imaging confirmation, thermal ablation was delivered for 15 minutes at 85°C to create an approximately 1 cm spherical lesion within each treated vertebral body (Fig. 2). Detailed information about the surgical technique was previously described in the literature [14]. All of the study investigators had training and previous experience with percutaneous transpedicular cannulation, such as pedicle screw placement, vertebroplasty, and/or kyphoplasty; all received cadaver training on the BVN RF ablation procedure before study initiation.

Patients randomized to standard care continued treatment, including, but not limited to, pain medications, physical therapy, exercise, chiropractic treatment, acupuncture, and spinal injections. Standard care was provided in a shared decision-making process between the patient and the treating investigator, according to the investigator's medical judgment and the patient's clinical presentation and experiences with prior treatments.

Study follow-up

The primary endpoint of the study is collected at 3 months postrandomization (standard care) or post-treatment (RF ablation). In addition, all RF ablation patients are followed at 6 weeks, and 3, 6, 9, 12, and 24 months. Standard care patients are followed at 3, 6, 9, and 12 months. Here, results from the 3-month primary endpoint are reported.

Target success

Magnetic resonance imaging (T1, T2, and STIR time constants) was performed at 6 weeks post RF ablation. Measurements of the degree of overlap between the RF ablation lesion and the terminus of the BVN for each vertebral body were performed by an independent, blinded neuroradiologist reviewer. Targeting success was based on a defined threshold of observed overlap.

Outcome measures

Patient-reported clinical outcomes were evaluated at baseline and 3, 6, 9, and 12 months using validated questionnaires, with 3-month outcomes reported here. Functional impact was measured using the Oswestry Disability Index (ODI) questionnaire [16]. Low back pain was assessed using a Visual Analog Scale (VAS) [17] ranging from 0 (no pain) to 10 (worst pain imaginable). Health Status and Quality of Life were measured at each follow-up using the SF-36 [18] and EQ-5D-5L [19,20] questionnaires. Physical and neurological examinations were performed by the site investigator(s) at each follow-up study visit. Spinal and neurological adverse events (AEs) were collected at each study visit. All reported AEs were adjudicated by an independent clinical event committee for relatedness to device therapy and procedure.

The predefined primary endpoint of this study is the 3-month follow-up, and the primary outcome is a between-arm comparison of the least squares (LS) mean change in

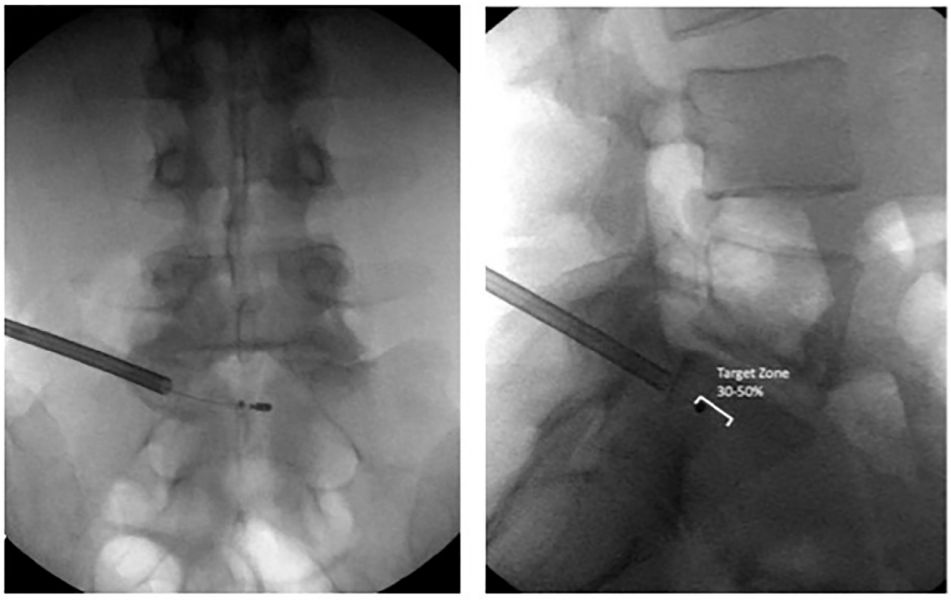

Fig. 1. Fluoroscopic images showing probe placement at S1. (Left) AP Image. (Right) lateral image with target zone.

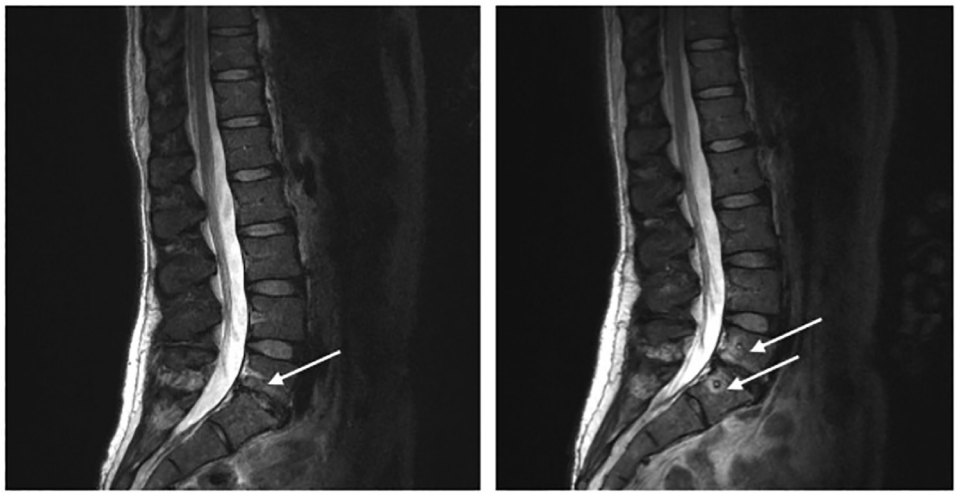

Fig. 2. Example of pre and post treatment T2-weighted MRI. (Left) Baseline MRI showing Modic changes at L5–S1 vertebral endplates. Arrow points to terminus of BVN at L5. (Right) Six-week post-treatment MRI arrows showing RF ablation lesion.

ODI from baseline to 3 months post-treatment, adjusted for baseline ODI.

Sample calculations

The full study was over-powered at 95% power to detect a 10-point difference in ODI with a two-sided overall alpha level of 0.05, requiring 150 randomized participants (approximately 75 participants per arm) with an estimated attrition rate of 15%. The actual attrition rate was much lower, thereby requiring less participants to be enrolled. At 100 randomized participants (approximately 50 per arm), the study was 80% powered to detect a 10-point difference with a two-sided overall alpha level of 0.05. The study had a group-sequential design with one planned interim analysis for primary endpoint superiority testing after 60% of the randomized participants completed their 3-month follow-up visit. These results are presented herein. Statistical significance was defined as $p < .025$ for this interim analysis for an overall alpha level of 0.05.

Statistical analysis

All study outcomes data were analyzed as intent to treat. Statistical analysis was performed with SAS version 9.3 software (SAS Institute Inc, Cary, NC, USA), using an analysis of covariance (ANCOVA) with a factor of treatment group and a covariate of baseline ODI score for the primary endpoint, producing LS means for statistical comparison. Values were adjusted for multiple imputation. Missing values were imputed using multiple imputations, and only one participant had missing data for the primary outcome. Responder rates were analyzed using Fischer's Exact test without imputation for missing values. Secondary endpoint estimates and p values were analyzed using an ANCOVA with a factor of treatment group and covariate of the baseline scores for each of the endpoints for between arms comparisons.

Study revisions

The protocol was revised to allow treatment of up to four vertebrae in nonconsecutive levels from L3 to S1 upon receiving Food & Drug Administration 501k clearance. Inclusion of patients at least 6 months from laminectomy or discectomy, with moderate symptomatic spinal stenosis, and taking extended-release opioids was also allowed. All subjects met the inclusion/exclusion criteria of the final protocol for the analysis. An evaluation of the impact of protocol revisions to the primary endpoint was conducted with no significant differences detected, and no adjustment for differences was required.

Results

Planned interim analysis and DMC decision to halt enrollment

As per the study protocol, interim analysis was undertaken when 60% of patients reached the 3-month follow-up, the primary endpoint of the study. At the time of the independent DMC's review of the prespecified interim analysis, a total of 140 patients were randomized, with 104 patients (n=51 RF ablation and n=53 standard care) having completed their 3-month follow-up. Thus, there was <1% attrition at the primary endpoint (Fig. 3). The interim analysis showed statistical superiority ($p<.001$) for all patient-reported outcome measures favoring the RF ablation arm. This resulted in a recommendation from the DMC to halt enrollment in the study and offer patients in the standard care arm early cross-over to the RF ablation arm.

There were three members of the DMC—1 independent statistician and 2 independent physicians (an interventional radiologist and an anesthesiologist). The physician qualifications to serve on the DMC were: independence from the sponsoring company with no current or previous financial relationships; international recognition in spine care with

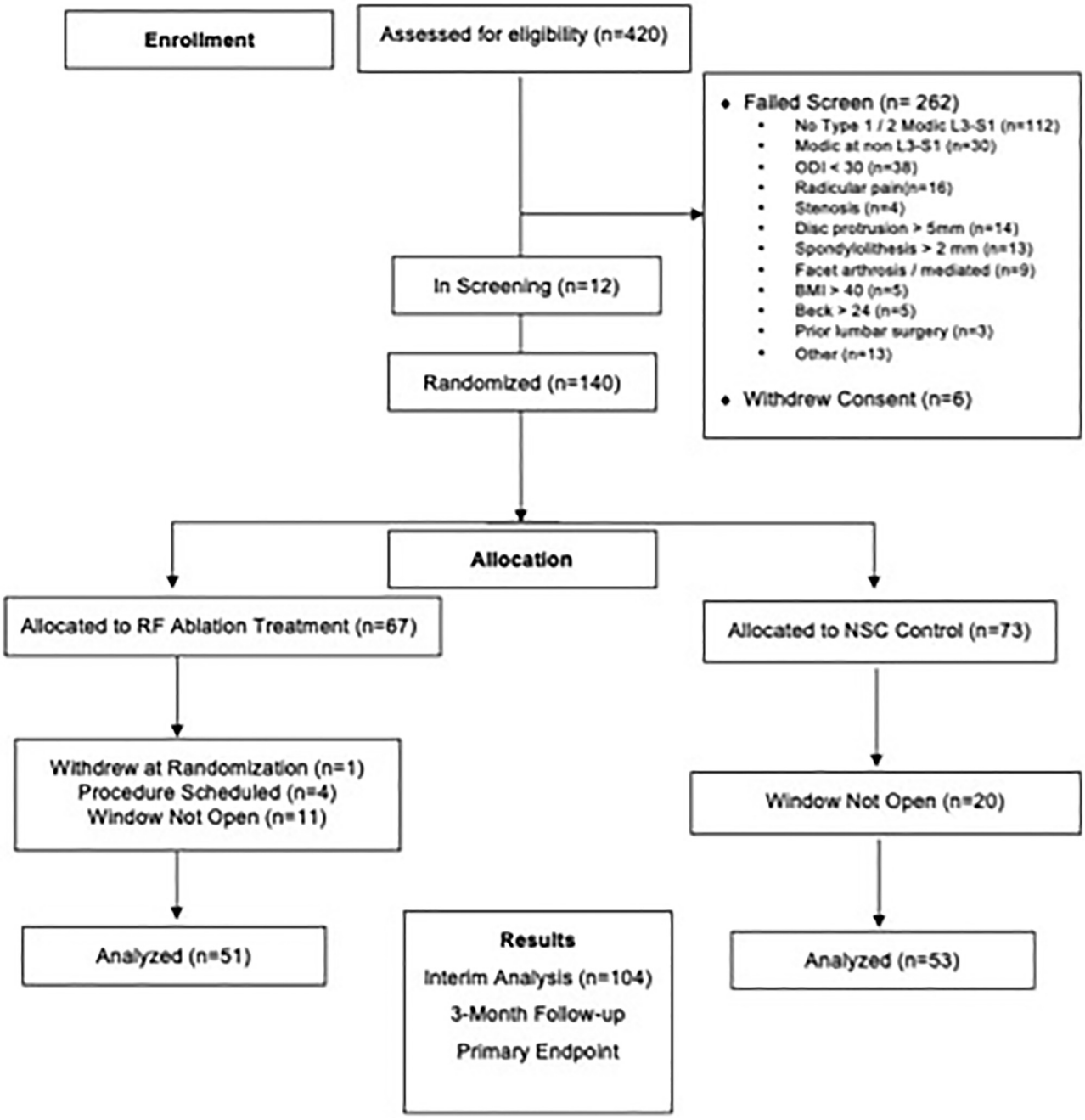

Fig. 3. Consort flow of study patients at the time of the predetermined 3-month interim analysis.

clinical expertise in invasive spine treatments; extensive experience with scientific studies, including acting as principle investigators of studies, acting on the editorial board of journals, and in-depth understanding of statistics.

To make their recommendations the DMC reviewed the same outcomes reported in this study. The DMC Charter and statistical analysis plan prespecified effectiveness superiority as $p<.025$. There were no safety concerns noted by the DMC. However, the DMC noted the overwhelming degree of superiority in the treatment arm combined with the requirement that subjects have chronic LBP for a minimum of 6 months with conservative treatment and determined that it was not ethical to continue the control arm and that further enrollment into the treatment arm was not needed.

Patient demographics & baseline characteristics

Demographics and baseline characteristics were similar between the two groups (Table 2). Baseline ODI was 46.1 (p=.064); VAS was 6.67 (p=.231); mean age was 50 years (p=.098). The percentage of patients with LBP symptoms

Table 2
Depicts the demographics and baseline characteristics of the ITT interim study population

	Interim Total (N=104)	RF Ablation (N=51)	Standard Care (N=53)	p Value
Mean Age (years), SD (Range)	50.0, 10.1 (26–70)	50.0, 9.0 (32–68)	50.0, 11.1 (26–70)	.0977†
Male, n (%)	51 (49.0%)	26 (51.0%)	25 (47.2%)	.845*
Mean BMI (kg/m*), SD (Range)	28.1, 4.7 (18.9–39.5)	27.9, 4.5 (18.9–38.4)	28.2, 5.0 (19.6–39.5)	.720†
Current tobacco use – n (%)	9 (8.7%)	6 (11.8%)	3 (5.7%)	.589[2]
Caucasian n (%)	97 (93.3%)	49 (96.1%)	48 (90.6%)	.437*
Married n (%)	74 (71.2%)	33 (64.7%)	41 (77.4%)	.195*
College degree or higher n (%)	52 (50.0%)	28 (54.9%)	24 (45.3%)	.842*
Working before procedure n (%)	82 (78.8%)	43 (84.3%)	39 (73.6%)	.232*
Not working due to back pain n (%)	4 (3.8%)	3 (5.9%)	1 (1.9%)	.358*
Mean BDI, SD (Range)	5.9, 4.84 (0–20)	6.0, 5.08 (0–20)	5.8, 4.64 (0–16)	.858†
Duration low back symptoms n (%)				
≥6 months to <1 year	6 (5.8%)	4 (7.8%)	2 (3.8%)	
≥1 year to <2 years	3 (2.9%)	3 (5.9%)	0 (0.0%)	
≥2 years to <3 years	12 (11.5%)	5 (9.8%)	7 (13.2%)	
≥3 years to <5 years	13 (12.5%)	7 (13.7%)	6 (11.3%)	
≥5 years	70 (67.3%)	32 (62.7%)	38 (71.7%)	.404*
Treatment history n (%)				
Opioid use at baseline	33 (32%)	18 (35.3%)	15 (28.3%)	.529*
Injections	73 (70.2%)	31 (60.8%)	42 (79.2%)	.054*
Past lower pack surgeries	12 (11.5%)	6 (11.8%)	6 (11.3%)	1.000*
Disc protrusion (1 or more levels), n %	60 (57.7%)	30 (58.8%)	30 (56.6%)	.845*
Grade 1 spondylolithesis n (%)	8 (7.7%)	6 (11.8%)	2 (3.8%)	.157*
Type of Modic by subject n (%)				
Type 1,	38 (36.5%)	18 (35.3%)	20 (37.7%)	.634*
Type 2	55 (52.9%)	29 (56.9%)	26 (49.1%)	
Mixed (Type 1 & Type 2)	11(10.6%)	4 (7.8%)	7 (13.2%)	
Baseline mean ODI, *SD (Range)*	46.1, 11.30 (30–88)	44.0, 11.08 (30–70)	48.1, 11.24 (32–88)	.064†
Baseline mean VAS, *SD (Range)*	6.67, 1.33 (4.0–10.0)	6.51, 1.31 (4.0–10.0)	6.82, 1.34 (4.0–10.0)	.231†
Baseline mean SF-36 PCS, *(Range)*	32.04 (17.23–47.64)	32.79 (18.43–46.93)	31.33 (17.23–47.64)	.301†
Baseline mean EQ-5D-5L, *(Range)*	.6207 (0.252–0.827)	.6322 (0.270–0.827)	.6095 (0.252–0.827)	.378†

BDI, Beck Depression Inventory; PCS, physical component summary; EQ-5D-5L, EuroQual Group 5 Dimension five-Level Quality of Life.
* p value from Fischer's Exact test.
† p value from a two sample *t* test with a factor of treatment group.

≥5 years was 67.3% (p=.404). Over 70% (p=.831) of patients had previously undergone at least one trial of physical therapy or a formal exercise program; 42% (p=.692) had received chiropractic care; 70% (p=.054) had undergone spinal injections, with 16% (p=.434) having undergone prior RF ablation of a facet or sacroiliac joint(s). Prior usage of medications was also similar.

Treatment results

Treatment was completed in all 51 RF ablation patients. Two-vertebral bodies were treated in 40 subjects and three vertebral bodies in the remaining 11 subjects. The most commonly treated segment was L5–S1 (24 patients, 47%), followed by L4–L5 (29%), and L4–L5–S1 (18%). Mean procedure duration was 92.5 minutes (SD 38.82) from incision to closure. In regard to health-care utilization, no RF ablation patients received a spinal injection before the 3-month end-point, whereas in the standard care arm, six standard care patients (11%) received injections across five study sites. Opioid pain medications were used by 32% (p=.529) of patients at baseline and no significant difference in opioid reduction was observed between the two treatment arms at 3-months.

ODI (primary outcome)

The primary outcome was a between-arm comparison of the LS mean change in ODI from baseline to 3 months post-treatment, adjusted for baseline ODI. At 3-months, the mean change in ODI from baseline was −25.3 points in the RF ablation arm, compared with −4.4 points in the standard care arm (Fig. 4). The difference between arms was −20.9 points as shown in Table 3 (p<.001). Using a 10-point improvement threshold for success, 74.5% of patients in the RF ablation arm reached clinical success compared with 32.7% of patients in the standard care arm as shown in Fig. 5 (p<.001). An ODI improvement of ≥20 points was reported by 62.7% of RF ablation patients compared with 13.5% in standard care patients (p<.001).

VAS

Visual Analog Scale and other secondary outcomes are displayed in Table 4. The LS mean change in VAS from

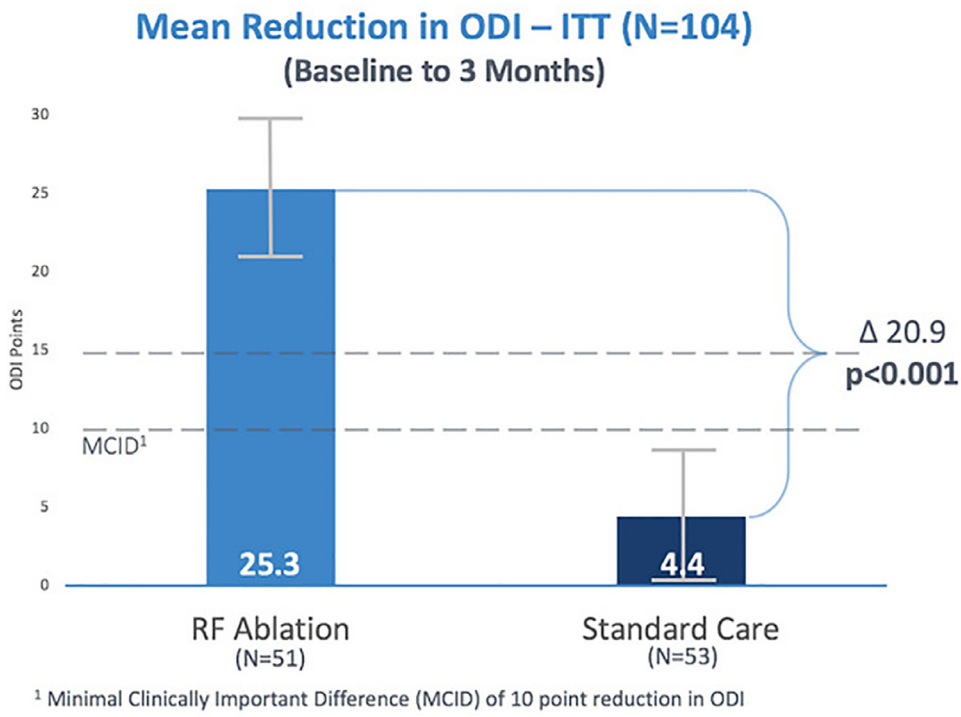

Fig. 4. Mean reduction in ODI-ITT (N=104).

baseline was −3.46 in the RF ablation arm, compared with −1.02 in the standard care arm (Fig. 6). The mean difference between arms was −2.44 (p<.001). Using a threshold of 2.0 cm improvement, 72.5% of patients in the RF ablation arm reached clinical success compared with 34.0% of patients in the standard care arm as shown in Fig. 7 (p<.001).

Table 3
ODI was the primary outcome of the pre-planned interim analysis at 3 months, the primary endpoint of the study. This table depicts the details of the primary outcome

	RF Ablation (N=51)	Standard Care (N=53)	p Value
Baseline ODI (0−100 points)			
Mean, SD,	44.0, 11.08	48.1, 11.24	.064*
Median (Range)	40.0 (30−70)	36.0 (32−88)	
3-month ODI (0−100 points)†			
Mean, SD,	19.9, 16.59	42.5, 15.83	
Median (Range)	18.0 (0−62)	40.0 (10−74)	
Mean change in ODI baseline to 3-months			
Mean, SD,	−24.1, 18.97	−5.6, 14.33	
Median (Range)	−26.0, (−70 to 12)	−2.0, (−64−20)	
LS Mean change in ODI baseline to 3-months			
LS mean	−25.3	−4.4	
95% confidence interval‡	(−29.6 to −21.0)	(−8.7 to −0.2)	
Mean difference between arms			
LS mean adjusted for baseline ODI	−20.9		<.001‡
Confidence intervals‡	−27.0 to −14.7		

* p value from a two sample *t* test with a factor of treatment group.
† 3 month visit is computed as post-treatment for the RF Ablation Arm, and postrandomization for the Control Arm. Multiple imputation used to impute missing values.
‡ Estimates and p value from an ANCOVA with a factor of treatment group and a covariate of baseline score. Values have been adjusted for multiple imputation.

SF-36 and EQ-5D-5L

The LS mean change from baseline between the RF ablation and standard care arms, respectively, in SF-36 (mental) were 2.615 versus −2.786; and SF-36 (physical) were 14.021 versus 2.114. The difference between arms in adjusted means were both statistically significant (p<.001). Similarly, LS mean change from baseline in EQ-5D-5L was 0.1803 in the RF ablation arm and 0.0135 in the standard care arm, resulting in an adjusted mean difference between arms of 0.1668 (p<.001).

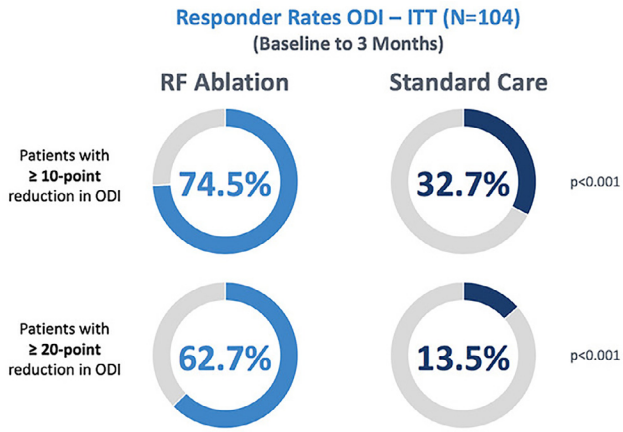

Fig. 5. Responder rates ODI-NIT (N=104).

Table 4
The secondary outcomes of the preplanned interim analysis at 3 months. The table depicts the details of the secondary outcomes; all showed a statistically significant difference between arms (p<.001)

	RF ablation (N=51)	Standard care (N=53)	p Value
ODI responder rates			
≥10-point reduction in ODI, *n (%)*	38 (74.5%)	17 (32.7%)	<.001*
≥20-point reduction in ODI, *n (%)*	32 (62.7%)	7 (13.5%)	<.001*
Baseline VAS (0–10 cm)			
Mean, SD,	6.51, 1.310	6.82, 1.339	
Median, (Range)	6.50, (4–10)	7.00, (4–10)	
3-month VAS (0–10 cm)			
Mean, SD,	3.11, 2.636	5.73, 2.155	
Median, (Range)	2.00, (0–10)	6.00, (0–10)	
Mean change in VAS baseline to 3-months			
Mean, SD,	−3.40, 2.586	−1.08, 2.082	
Median, (Range)	−4.00, (−8.0–2.0)	−1.00, (−6.5–3.0)	
LS mean change in VAS baseline to 3-months			
LS Mean	−3.46	−1.02	
95% confidence interval†	(−4.10 to −2.82)	(−1.66 to −0.37)	
Mean difference between arms			
LSM mean adjusted for baseline VAS	−2.44		<.001†
Confidence intervals†	(−3.36 to −1.53)		
VAS responder rates			
≥1.5 cm reduction in VAS, *n (%)*	38 (74.5%)	18 (36.0%)	<.001*
≥2.0 cm reduction in VAS, *n (%)*	37 (72.5%)	17 (34.0%)	<.001*
Baseline SF-36 (PCS)			
Mean, SD,	32.78, 6.83	31.33, 7.48	
Median range	32.42 (18.43 −46.93)	30.18 (17.23–47.64)	
LS mean change in SF36 (PCS) Baseline to 3-months			
LS mean	14.021	2.114	
95% Confidence interval†	(11.995–16.048)	(0.088–4.140)	
Mean difference between arms SF-36 (PCS)			
LSM mean adjusted for baseline SF-36 PCS	11.907		<.001†
Confidence intervals†	(9.035–14.780)		
Baseline SF-36 (MCS)			
Mean, SD,	53.51, 9.39	52.31, 9.51	
Median Range	54.76 (22.24–69.80)	54.46 (29.43–64.67)	
LS mean change in SF36 (MCS) Baseline to 3-months			
LS mean	2.615	−2.786	
95% Confidence interval†	(0.450–4.781)	(−4.952 to −0.620)	
Mean difference between arms SF-36 (MCS)			
LSM mean adjusted for baseline SF-36 MCS	5.401		<.001†
Confidence intervals†	(2.333–8.469)		
Baseline EQ-5D-5L			
Mean, SD,	0.6322, 0.1290	0.6095, 0.13227	
Median range	0.6430 (0.270–0.827)	0.6340 (0.252–0.827)	
LS mean change in EQ-5D-5L baseline to 3-months			
LS mean	0.1803	0.0135	
95% Confidence interval†	(0.1469–0.2137)	(−0.0203–0.0472)	
Mean difference between arms			
LS mean adjusted for baseline EQ-5D-5L	0.1668		<.001†
Confidence intervals†	(0.1193–0.2144)		

PCS, physical component summary; MCS, mental component summary; EQ-5D-5L EuroQual Group 5 Dimension 5-Level Quality of Life.

* p Value from a Fisher's exact test.

† Estimates and p value from an ANCOVA with a factor of treatment group and a covariate of baseline score.

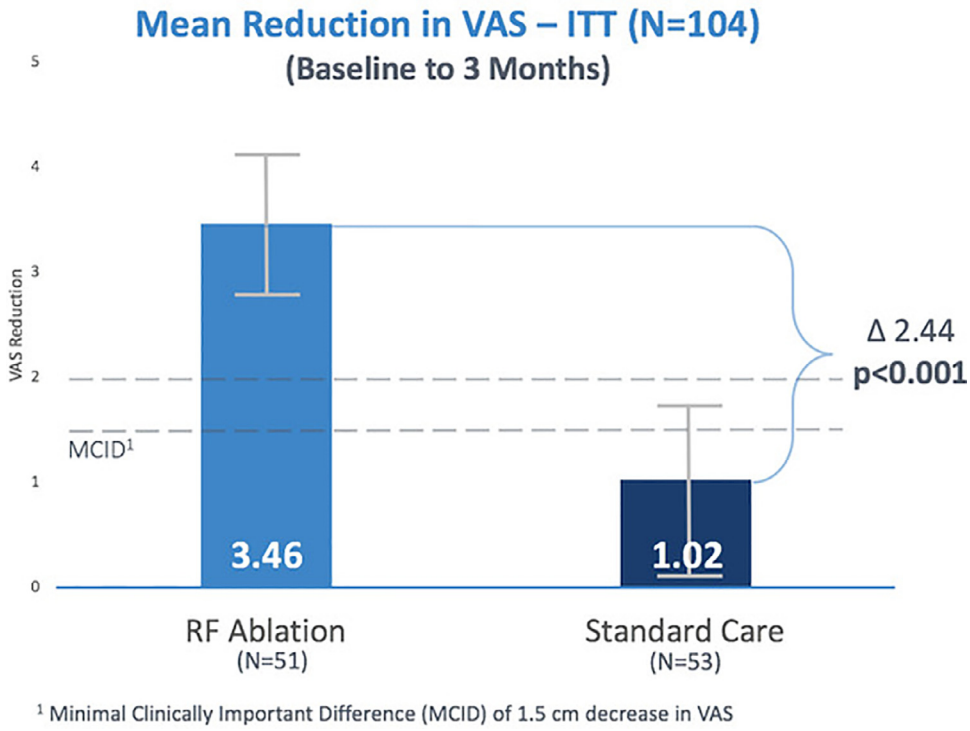

Fig. 6. Mean reduction in VAS-ITT (N=104).

Patient satisfaction

Fifty of the 51 RF ablation arm patients responded to a series of questions related to satisfaction following the procedure. Thirty-nine patients (78%) rated their condition as improved; 8 patients (16%) reported no change; and 3 patients (6%) indicated worsened condition. Thirty-seven patients (74%) felt the treatment was a success and were satisfied with the results of surgery; Forty patients (80%) would have the surgery again for the same condition, and 44 (88%) would recommend the procedure to a loved one with the same condition.

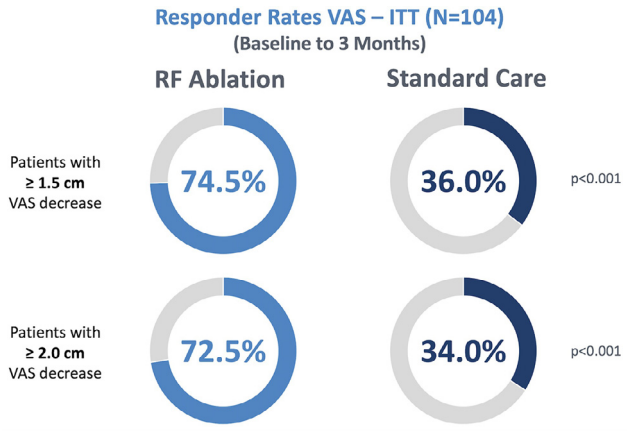

Fig. 7. Responder rates VAS-ITT (N=104).

Target success

Targeting was adjudicated as successful in 96% of patients (49 of 51 subjects) and in 98% of treated vertebral bodies (111 of 113 vertebral bodies). Targeting failure was observed in two patients. The first demonstrated failure in one of two treated vertebrae, and the second in one of three treated vertebrae. With only two target failures in the study, a statistical comparison is not possible. However, a qualitative comparison does suggest a potential impact on outcomes, with outcomes below the treatment group mean and proportional to the individual target failure rate. Specifically, worse outcomes occurred in the first participant with the higher failure rate (ODI +10 points and VAS +1 point) relative to the second participant with the lower failure rate (ODI -10 points, and VAS -4 points).

Adverse events

Adverse events that were musculoskeletal, neurological, device or procedure related were collected in this study. Of the 22 AEs reported and adjudicated, 15 were in 13 RF ablation treated patients. Regarding AEs in the RF ablation arm, none were deemed device related. Three were categorized as general procedure related (incisional pain, urinary retention, and lateral femoral cutaneous neurapraxia). Seven were felt to be procedure related. One patient had back pain in a new location and the remaining 6 patients had either leg pain or paresthesia. All were categorized as mild, requiring no interventions beyond oral medication. Five of the seven AEs resolved before the 3-month

follow-up visit (mean of 41 days). Two are ongoing at the time of this report (one mild paresthesia, one new leg pain that was reported 6-months postprocedure). There were no broken devices, no pedicle fractures, and no infections. One patient in the RF ablation arm was rescheduled due to inadequate analgesia under monitored anesthesia care. That patient was successfully treated at a later date without incident under general anesthesia.

Discussion

This report details the results from a preplanned interim analysis of outcomes at the 3-month primary endpoint comparing BVN ablation to standard nonoperative care in patients with CLBP and Modic Type 1 or Type 2 changes from L3 to S1. The primary outcome was determined by changes in patient-reported function on the ODI and was strongly in favor of the RF ablation treatment group with a mean improvement of −25.3 points, and an adjusted difference between means of −20.9 points compared with the usual care group (Table 3). These differences were statistically significant and well above established thresholds for clinical significance. The same is true of the study's secondary outcomes including pain, health status, quality of life, and patient satisfaction (Table 4).

Although this study reports the 3-month primary outcomes from the planned interim analysis, and enrollment has stopped, long-term follow-up continues. Results of this interim analysis were compelling enough to halt study enrollment and initiate an early crossover option for patients in the control arm, based on the recommendations of the independent data management committee. It is surprising for a LBP treatment study to be halted early due to better than expected results. In fact, the authors are unaware of another instance in recent decades. We speculate that this highly successful outcome is due to a combination of factors. Most importantly, our protocol included the treatment of a well-defined subpopulation of CLBP patients using a novel intervention that targets a radiographically identifiable pathoanatomic process elucidated by ample basic science.

By contrast, common therapies aimed at chronic nonspecific LBP are limited by small effect size [4] leaving many patients dissatisfied [22]. Clinicians and researchers in the spine care community have long recognized these challenges and have identified the heterogeneous nature of the large CLBP population as an important contributor. Accordingly, better identifying subgroups of CLBP might result in more targeted and effective treatments. The results of this study highlight the benefits of such an approach.

Magnetic resonance imaging is commonly used to identify potential sources of CLBP, however few MRI findings have proven reliable to improve CLBP treatment outcomes. The correlation between vertebral endplate (Modic) changes and LBP has been extensively investigated and the pathoanatomic basis of vertebrogenic back pain established [23–33]. Ample histologic, anatomic and immunohistochemical evidence supports the nociceptive role of the BVN in the pathogenesis of LBP [10,11]. In addition, a recent review concluded that Modic changes are more likely to be a reflection of a pathologic process than a coincidental finding, thus segments with Modic changes are a potential target for therapy [7]. Accordingly, this study enrolled subjects based on specific MRI findings, including Type 1 or Type 2 Modic changes (Table 1).

Comparison to the previously published RCT of BVN ablation

Both this study and the previous RCT on BVN ablation used the same clinical and radiographic inclusion and exclusion criteria and primary endpoint [14]. Still, some caution should be exercised in directly comparing the results of the current study with that of the previous sham-controlled RCT of BVN ablation, since different study designs and different control groups were used. Notwithstanding this caution, the 3-month outcomes in the BVN ablation treatment arms of both studies are similar with somewhat greater improvements in ODI and VAS in the current RCT relative to the previous sham-controlled trial. In addition to the trial design differences, this may be due to modifications of the access instruments that improved RF probe placement resulting in greater target success in the current study (96% vs. 89%). The 12-month and the 24-month results from the prior sham-controlled trial demonstrated that 3-month outcomes were maintained in the treatment arm [15]. It also revealed that opioid usage was reduced at 12-months in participants with improved pain and function [21]. Although the current study did not show a difference in opioid reduction at 3 months, this is not surprising given the different time points and the complexity of changing opioid habits.

Comparison to other treatments for chronic LBP

A strength of the current study is that it provides direct comparison to standard nonoperative care of CLBP, and thus demonstrates the potential benefits of BVN ablation relative to currently available alternatives for qualifying patients. The use of a standard care control arm is common in randomized trials of LBP treatments since the optimal care for CLBP remains unknown. Weinstein et al. suggested that variability in conservative treatment as prescribed by the treating physicians is a better reflection of actual clinical practice than a highly structured care program [34]. Fortunately, the existence of many studies using a standard care control provides the opportunity for additional insights through comparisons. It is important to note that such comparisons should be interpreted cautiously. By definition, standard care is intended to mimic real-world treatment and is not structured. Thus, differences in standard care between studies may influence comparisons.

When compared with a standard care control, treatment of patients with CLBP failed to demonstrate a statistically significant difference or failed to exceed established thresholds of clinical relevance using acupuncture [35], cognitive behavioral therapy [36], massage [37], multidisciplinary rehabilitation [38], and yoga [39]. The observed treatment outcomes in the current study are much better than the nonoperative treatments detailed above. Perhaps it is more appropriate to compare the treatment effect size of BVN ablation to other surgical treatments for CLBP. In this regard, a recent meta-analysis of seven studies comparing segmental fusion to different types of structured and unstructured care for CLBP revealed a weighted mean difference in ODI of 5.13 points (95% confidence interval 0.19−10.07) in favor of fusion surgery [40]. In comparison, the current study achieved a mean difference of 20.9 points.

Although these comparisons help provide perspective on the strength of the current study's results, they do not suggest that BVN ablation is a better treatment for all people with CLBP. Rather this study, and these comparisons, reveal that BVN ablation is a highly effective treatment only for a specific subgroup of patients with CLBP characterized by the clinical and radiographic criteria outlined in this study's methods.

Previous novel CLBP treatments have been associated with indiscriminant patient selection and overuse. This is partially explained by a scarcity of objective diagnostic standards, and further motivated by a lack of highly effective and available treatment options for the CLBP population at large. The authors believe that the success observed in the current study is a direct result of meticulous patient selection based on rigorous clinical and radiographic criteria and they caution against the broad application of this procedure to the general population with CLBP.

Limitations include use of a nonstructured standard care control and open label design. In addition, industry funding is a potential source of study bias. This report only provides short-term 3-month outcomes from the planned interim analysis and long-term results from the complete study cohort are underway. Although this study was designed to collect longer-term data from both randomized groups, a review of the study results from the planned interim analysis led to the independent DMC's recommendation to halt enrollment and offer early crossover to patients in the standard care group. It was noted that the Informed Consent regulations and the Declaration of Helsinki require that study participants be advised of any new information from the study that may impact their willingness to continue, and the results of the interim analysis would have such an impact, especially on the control group. Ultimately, the DMC determined that is was not ethical to continue the control arm, and that further enrollment into the treatment arm was not needed. As a result, follow-up will be limited in the standard care patients in the final analysis to results collected up to the point of cross-over or study exit. Further follow-up of the treatment arm patients for 5 years is underway as a single arm study, and control subjects that elect to crossover to treatment are being followed at 3 and 6 months postprocedure. Finally, another important limitation of this study is a lack of generalizability to the broader CLBP population who do not meet the strict clinical and radiographic criteria of this study.

Conclusions

The present study further defines the role of radiofrequency ablation of the BVN. We report on a large randomized controlled trial of patients with chronic LBP and type 1 or 2 Modic changes. Patients treated with RF ablation of the BVN exhibited significant improvement in ODI, VAS, SF-36, and EQ-5D-5L at 3 months. In addition, patients in the treatment arm were found to have higher satisfaction than in the control arm. This further demonstrates the role of this novel therapy in the treatment of a specific subtype of chronic LBP.

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