Randomized Pilot Study

Lumbar Medial Branch Cryoneurolysis Improves Pain and Function Versus Radiofrequency Ablation for Chronic Low Back Pain: 12-Month Randomized Pilot Study

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Background: Chronic low back pain (CLBP) is a common condition that can be treated with radiofrequency ablation (RFA). However, RFA can be destructive to tissue surrounding the targeted nerves. Cryoneurolysis is an alternative to RFA that applies cold temperatures to disrupt nerve conduction pathways via Wallerian degeneration, allowing for nerve regrowth.

Objectives: To compare the safety and efficacy of cryoneurolysis to RFA for treatment for CLBP.

Study Design: A randomized pilot study (NCT06016127) that received institutional review board approval from Advarra, Inc. (Pro00062787).

Setting: A single center in the United States.

Methods: Eligible patients with facet-mediated CLBP underwent lumbar RFA or cryoneurolysis of the lumbar medial branch nerve. The patients were originally followed for 180 days after treatment, with an optional study extension to 360 days. Study outcomes included pain scores on the numeric rating scale (NRS), functional disability status on the Oswestry Disability Index (ODI), Patient Global Impression of Change (PGIC) score, and safety. Analyses were adjusted for baseline NRS score, gender, and tobacco use.

Results: Age, body mass index, low back pain duration, and baseline ODI scores were similarly distributed between the cryoneurolysis and RFA groups (n = 15 each). At Days 180 and 360, cryoneurolysis was associated with significantly lower NRS pain scores vs. RFA (Day 180: least squares mean [LSM; 95% confidence interval (CI)], 3.1 [2.1-4.1] vs. 5.4 [4.3-6.4]; LSM difference [95% CI], -2.1 [-3.6, -0.5]; P = 0.01; Day 360: LSM [95% CI], 3.0 [1.4-4.7] vs. 6.1 [4.5-7.7]; LSM difference [95% CI], -2.7 [-4.7, -0.7]; P = 0.01). ODI scores were numerically lower in the cryoneurolysis group than in the RFA group at Day 180 (LSM [95% CI], 13.3 [8.9-17.7] vs. 18.1 [13.6-22.6]; LSM difference [95% CI], -4.8 [-11.4, 1.9]; P = 0.15) and significantly lower at Day 360 (LSM [95% CI], 10.1 [6.0-14.3] vs. 20.6 [16.5-24.7]; LSM difference [95% CI], -10.5 [-16.6, -4.3]; P = 0.002). The mean percent decrease in ODI score from the baseline was greatest at Day 360 in the cryoneurolysis group than in the RFA group (-21.7% vs. -4.0%; P = 0.42). More cryoneurolysis-treated patients than RFA-treated patients had "no disability" or "mild disability" at Day 360 (6/11 vs. 5/12). Cryoneurolysis was associated with lower PGIC scores vs. RFA at Day 180 (LSM [95% CI], 2.6 [1.6-3.7] vs. 3.6 [2.6-4.7]; LSM difference [95% CI], -0.98 [-2.5, 0.6]; P = 0.2) and Day 360 (LSM [95% CI], 1.7 [0.7-2.8] vs. 4.4 [3.3-5.4]; LSM difference [95% CI], -2.6 [-4.2, -1.1]; P = 0.002). After Day 180, 45.5% of patients (5/11) who underwent cryoneurolysis and 75% (9/12) who underwent RFA required more than one additional spinal injection. No serious adverse events were observed. One mild adverse event considered unrelated to study treatment was reported (a compression fracture in the cryoneurolysis group).

Limitations: The study was not blinded, and the short tip of the cryoneurolysis device restricted its use to patients with low body mass indexes. Longer device tips are in development.

Conclusions: At 12 months after treatment for CLBP, cryoneurolysis had a favorable safety profile and led to more significant improvements in pain and functional disability than did RFA. A large multicenter trial is warranted to further investigate the effects of cryoneurolysis on CLBP.

Key words: Chronic low back pain, facet-mediated low back pain, cryoneurolysis, cryoanalgesia, cryoablation, cryotherapy, radiofrequency ablation, pain management, medial branch block

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Chronic low back pain (CLBP) is a common condition that, in 2020, affected one in 13 people globally, or 619 million individuals (1). Low back pain of lumbar facet joints (facet-mediated low back pain) affects between 15% and 45% of patients with CLBP (2). Per the American Society of Pain and Neuroscience (ASPN) guidelines, CLBP is typically first treated conservatively, with physical therapy, exercise regimens, and pharmacological intervention (3). If these treatments are unsuccessful, other options are recommended, including injection therapy, surgical procedures (e.g., discectomy, fusion), intrathecal drug delivery, and conventional and cooled radiofrequency ablation (RFA) (3). The specific cause of CLBP is difficult to determine; therefore, guidelines suggest conservative measures and diagnostic medial branch nerve blocks be used before lumbar RFA is considered (3). Notably, the number of blocks to perform before RFA is not well established (3); it has been proposed that while one diagnostic medial branch nerve block may be sufficient to determine candidates eligible for RFA, 2 diagnostic medial branch nerve blocks may be better in clinical trial contexts in which the efficacy of RFA is being measured (4).

In an RFA procedure, the application of thermal energy (i.e., heat) destroys specific nerves to provide pain relief (5,6). Guidelines from the American Society for Interventional Pain Physicians and ASPN characterize evidence for the effectiveness of lumbar RFA in treating low back pain as moderate to strong, and prior randomized controlled trials in which patients have received RFA or a control treatment for facet-mediated CLBP corroborate this conclusion, with RFA leading to significant reductions in visual analog scale (VAS) scores for back pain (3,7-9). Despite the potential efficacy of RFA, the high temperature involved in the treatment can cause vascular injury, procedure-related pain, and destruction of tissue surrounding the targeted nerves (2,5,6,9). The incidence of neuritis after lumbar RFA ranges from one percent to 10%, with the duration of effects and need for treatment varying among patients (10). Steroid treatment can reduce the neuritis and injection-site tenderness that may result from RFA (11). However, ASPN guidelines indicate a low level of certainty for using steroids to treat pain and discomfort after RFA, since these effects are generally considered minor (6). Furthermore, injecting steroids to manage complications associated with RFA may not be appropriate for populations of patients who are vulnerable to steroid side effects (e.g., patients with diabetes or high blood pressure) (12). Finally, RFA is not recommended for patients with permanent pacemakers or defibrillators unless caution is taken because the function of these devices relies on electrical activity detection, which RFA may potentially disrupt (6,13). Bipolar RFA may be a safer option for these patients than monopolar RFA; other precautions can also be implemented so patients with pacemakers or defibrillators can receive RFA (6,13,14).

Cryoneurolysis is an alternative treatment to RFA in which cold temperatures (between -60°C and -88°C) are applied near the targeted nerve to create an ice ball, which disrupts nerve conduction pathways via Wallerian degeneration and preserves the epineurium, perineurium, and endoneurium, allowing for nerve regrowth (15-19). The ice ball produced by cryoneurolysis treatment is visible during imaging and less destructive to surrounding tissue than is RFA (20). Carbon dioxide and nitrous oxide are typically used for cryoneurolysis because their low boiling points prevent the treatment temperature from decreasing below -80°C, ensuring the preservation of surrounding structures (19). Because cryoneurolysis allows for regrowth, it is different from cryoablation, a procedure that uses more extreme cold temperatures (up to -196°C) to destroy nerve tissue permanently, which can also affect surrounding structures (19,21). Data regarding cryoneurolysis for the treatment of lumbar facet joint pain are limited, although some prospective studies demonstrated that patients with CLBP maintained pain relief for at least one year after the procedure (22-24). This pilot study was designed to assess the safety and feasibility of

cryoneurolysis versus those of RFA for the treatment of facet-mediated CLBP, including comparisons of pain and functional disability outcomes.

Methods

Study Design

This single-center, randomized pilot study compared the safety and feasibility of lumbar medial branch cryoneurolysis to those of RFA for facet-mediated CLBP (NCT06016127). Advarra, Inc. (Pro00062787) issued institutional review board approval on April 26, 2022. All patients provided informed consent. The study was conducted from June 16, 2022, to October 2, 2023. The study was originally planned to end at Day 180; however, after the 6-month data were obtained, a study extension to Day 360 was requested and granted.

Patients

Adult patients were eligible if they met the following inclusion criteria: having CLBP (of > 3 months' duration), being afflicted with a primary ailment of axial low back pain suggestive of unilateral or bilateral facet joint involvement (i.e., facet-mediated CLBP), having a low back pain score of ≥ 4 on a numeric rating scale (NRS) of 0 to 10 or functional impairment at screening, and showing a lack of response to at least 3 months of nonoperative therapy (e.g., physical therapy, chiropractic care, spinal injections, nonsteroidal anti-inflammatory drugs, or other analgesics). Additionally, individuals must have had one of the following before screening: (1) 2 positive diagnostic medial branch blocks with local anesthetic only (e.g., no steroids) under fluoroscopic guidance that resulted in ≥ 50% relief of primary (index) pain (as measured by a ≥ 50% reduction in NRS pain scores) for the duration of the use of the anesthetic, or (2) a history of a positive response to RFA treatment (≥ 6 months before enrollment).

Patients were excluded for having any of the following: active workers' compensation, personal injury, Social Security disability insurance, or other litigation/compensation related to the spine; serious spinal disorders that may have affected outcomes (e.g., suspected cauda equina syndrome, infection, tumor, traumatic fracture, systemic inflammatory spondyloarthropathy, lumbar radiculopathy/radiculitis, neurogenic claudication); prior lumbar spinal fusion surgery; a comorbidity that may have inhibited study participation (e.g., lumbar radiculopathy, neuropathic pain disorder); current pregnancy, current nursing, or plans to become pregnant; a known contraindication to study devices (e.g., cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, open and/or infected wounds at or near the treatment site, coagulopathy); habitus preventing usage of the 3.5-inch needle required for the cryoneurolysis study procedure; a severe chronic pain disorder; the presence of a spinal neurostimulator or intrathecal analgesic drug pump; a poorly controlled mental illness (e.g., mood disorder, psychotic disorder); a history of other spine intervention/therapies in the 30 days before block administration (e.g., spinal injections, minimally invasive therapies, surgical therapies); a history of RFA in the low back region ≤ 6 months before study enrollment; or a history, suspicion, or clinical manifestation of alcohol abuse or dependence, illicit drug use, or opioid use or dependence (equivalent dose of ≥ 40 mg oral morphine per day in the past 30 days).

Procedures

Patients were screened within 30 days of the scheduled procedure, and participation was completed 360 (± 7) days after treatment. All patients finished 180 days of follow-up; some continued through 360 days after the study extension was granted. The patients were randomized one to one on the day of treatment (with a computer-generated code) to undergo either bilateral cryoneurolysis or RFA. Needle placement occurred at the L4, L5, and S1 sacral levels to target the L3 medial branch, L4 medial branch, and L5 dorsal ramus branch, respectively. Both cryoneurolysis and RFA were administered in the lumbar spine bilaterally at target medial branch nerves that encompassed one level above and below the involved vertebral levels. Patients were offered 2-4 mg of intravenous midazolam for sedation before the procedure.

Cryoneurolysis was administered with the iovera° system (Pacira BioSciences, Inc.) and the 190 Smart Tip (Pacira BioSciences, Inc.). The right L4, L5, and S1 articular pillars were identified through the use of fluoroscopy at each level, and the target points were located. A skin wheal was formed by injecting a mixture of 5 mL of one percent lidocaine, 2.5 mL of 0.5% bupivacaine, and 2.5 mL of normal saline over the target subcutaneously and deeply. Under fluoroscopic guidance, an 18-gauge, 6.35-cm introducer needle was inserted, using a 15-degree oblique view and a 15-degree caudad angle onto the superior articular process at the junction with the transverse process where the medial branch nerve lay at each level. Anterioposterior and oblique neuroforamen views confirmed

that positioning was outside of the neuroforamen and in the correct position at each level (Fig. 1A). The Smart Tip was advanced completely into the introducer needle so it was flush with the latter needle's tip. The cryoneurolysis device was activated to produce cryoneurolysis using a 106-second cycle, which consisted of a 60-second treatment step with a one-second prewarming step and a 45-second postwarming step. The aforementioned procedure was then repeated on the other side.

RFA was administered with a Cosman G4™ Generator (Boston Scientific). For each procedure, a grounding pad was placed on the patient's upper thigh. The identification of the right L4, L5, and S1 articular pillars and the formation of the skin wheal were performed in the same manner as in the cryoneurolysis group. The practitioner inserted a 20-gauge, 10-cm needle with a 10-mm active tip at a 15-degree oblique view and a 15-degree caudad angle onto the waist of each pillar at each level under fluoroscopic guidance and used anteroposterior and oblique neuroforamen views to confirm that positioning was outside of the neuroforamen and in the correct position at each level (Fig. 1B). The site was stimulated at 50 Hz up to 1.5 volts, and recordings confirmed proper needle placement with no stimulation of the sensory or motor roots. A mixture of 3 mL of 0.25% bupivacaine, 2 mL of one percent lidocaine, and 1 mL of 40 mg/mL triamcinolone was divided and injected at each level. Stimulation was applied at each level at 80°C for 60 seconds to create the lesions.

After treatment, patients received daily follow-up calls on Days one through 6 and on Days 7, 15, 60, 90, 120, 150, 210, 240, 270, 300, 330, and 360. Data for Day 210 were not collected for most patients because the study extension request was under evaluation; therefore, Day 210 data are not reported. Patients in both groups each received calls from one study administrator, and each study administrator applied the same criteria within the follow-up process. The patients attended follow-up visits on days 30 and 180. During the follow-up visit on Day 30, patients underwent a physical examination and may have undergone additional clinical assessments, and any need for additional interventional procedures was assessed. After Day 180, only major joint injections, bursa injections, and injections to spinal regions not part of the lumbosacral spine were permitted.

Outcomes

Pain intensity was measured from the baseline (i.e.,

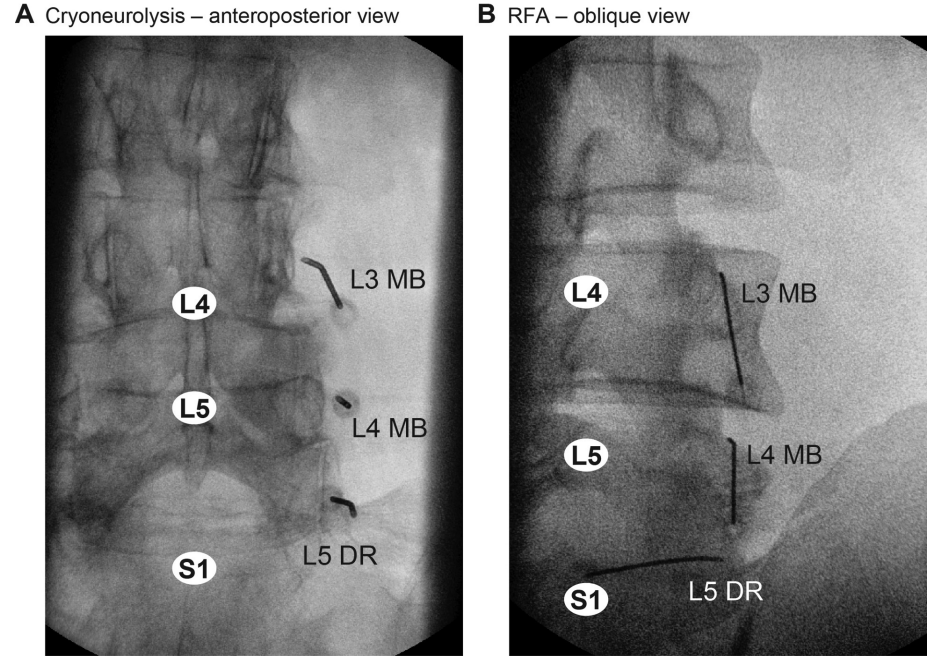

Fig. 1. *Fluoroscopic images of (A) cryoneurolysis needle placement from an anteroposterior view at L4, L5, and S1 sacral levels to target the L3 medial branch (MB), L4 MB, and L5 dorsal ramus (DR) branch, respectively, and (B) RFA needle placement from an oblique view at L4, L5, and S1 sacral levels to target the L3 MB, L4 MB, and L5 DR branch, respectively.*
RFA, radiofrequency ablation.

pretreatment) through Day 360 on an 11-point NRS (0 ["no pain"] to 10 ["worst possible pain"]) as "average pain over past 24 hours in the lower back." Additionally, at follow-ups from Day 30 through Day 360, study administrators ascertained patient disability with the Oswestry Disability Index (ODI; score range from 0 to 50 [0-4, "no disability"; 5-14, "mild disability"; 15-24, "moderate disability"; 25-34, "severe disability"; 35–50, "completely disabled"]) (25-27), Patient Global Impression of Change (PGIC) scores (score range from 0 ["much better"] to 10 ["much worse"]), and patient satisfaction with pain management (score range from one ["extremely dissatisfied"] to 5 ["extremely satisfied"]). The following definitions of treatment success and failure for cryoneurolysis and RFA were used at Day 360, as previously established: full success if pain is reduced to 50% or less of pretreatment levels, partial success if pain is reduced to between 51% and 69% of pretreatment levels, and failure if pain is reduced to 70% of pretreatment levels or greater (23). Safety outcomes included incidence of adverse device effects, serious adverse device effects, adverse events (AE), and serious adverse events (SAE) through Day 360.

Statistical Analyses

Because this pilot study was not formally designed to assess efficacy, formal hypothesis testing was not performed, and sample size was not calculated on the basis of statistical power to detect a treatment effect. Continuous variables were summarized with descriptive statistics, and categorical variables were tabulated with the number and percentage of unique patients. Least squares means (LSMs) of the "average pain over past 24 hours" NRS scores at Day 360 were calculated for each patient and summarized by treatment group. A linear regression model with adjustment for baseline NRS, gender, and tobacco-use status was used to test for significant differences between the cryoneurolysis and RFA groups. All tests were 2-sided, with a significance level of 0.05, and all analyses were performed with SAS Version 9.4 (SAS Institute).

Results

Study Participants

Of the 30 total patients, 15 received RFA, and 15 received cryoneurolysis. After the diagnostic nerve block administered before study treatment, the mean (SD) percentage of relief was 87.3% (18.0%) for patients in the cryoneurolysis group and 95.0% (10.8%) for patients in the RFA group. Age, body mass index, back pain duration, and baseline ODI scores were similarly distributed between groups (Table 1). Patients in both groups had received spinal injections within the last 12 months. In both groups, 93% of patients had received lumbar spine injections. After 180 days, 12 patients in the RFA group and 11 patients in the cryoneurolysis group continued in the follow-up extension period (Fig. 2). There were no differences in baseline characteristics or outcomes at 180 days between participants who remained in the study and those who dropped out.

Pain Outcomes

Adjusted LSM NRS pain scores were numerically higher in patients who had received RFA than in pa-

Table 1. *Patient demographics and baseline characteristics*.

	RFA (n = 15)	Cryoneurolysis (n = 15)	Total (n = 30)
Age, mean (SD), y	63.1 (12.7)	66.0 (17.1)	64.5 (14.9)
Gender, n (%)			
Male	7 (46.7)	9 (60.0)	16 (53.3)
Female	8 (53.3)	6 (40.0)	14 (46.7)
BMI, mean (SD), kg/m^2	28.1 (5.0)	26.5 (6.4)	27.3 (5.7)
White race, n (%)	15 (100.0)	15 (100.0)	30 (100.0)
Not Hispanic or Latino, n (%)	15 (100.0)	15 (100.0)	30 (100.0)
Duration of low back pain, mean (SD), y[a]	19.6 (16.2)	24.9 (19.7)	22.7 (18.2)
ODI score, mean (SD)	18.7 (5.9)	18.5 (7.1)	18.6 (6.4)
Average pain score over 24 hours on NRS, mean (SD)	7.1 (1.6)	6.5 (1.9)	6.8 (1.8)
Spinal injection history			
Any spine injections, n (%)	14 (93.3)	15 (100.0)	29 (96.7)
Lumbar spine	14 (93.3)	14 (93.3)	28 (93.3)
Cervical	1 (6.7)	3 (20.0)	4 (13.3)
Sacrum	1 (6.7)	1 (6.7)	2 (6.7)
Lumbar spine injection, n (%)			
Epidural	4 (26.7)	9 (60.0)	13 (43.3)
Facet	10 (66.7)	12 (80.0)	22 (73.3)
Other	1 (6.7)	0	1 (3.3)

BMI, body mass index; ODI, Oswestry Disability Index; RFA, radiofrequency ablation.
[a]RFA (n = 10); cryoneurolysis (n = 14); total (n = 24).

tients who had received cryoneurolysis after Day 7 of treatment (Fig. 3). The LSM difference (95% CI) between cryoneurolysis recipients and RFA recipients at Day 180 was -2.1 (-3.6, -0.5; P = 0.01) and at Day 360 was -2.7 (-4.7, –-.7; P = 0.01). Pain scores were significantly lower in the cryoneurolysis group than in the RFA group at Days 180, 300, 330, and 360 after treatment ($P \leq 0.03$; Suppl. Table 1). The cryoneurolysis group had a higher percentage of treatment success (e.g., pain reduction to ≥ 50% of baseline levels) than the RFA group at both Days 360 (45.5% [5/11] vs. 16.7% [2/12]) and 180 (46.7% [7/15] vs. 20% [3/15]).

ODI Outcomes

Adjusted LSM ODI scores were numerically lower in cryoneurolysis recipients than in RFA recipients at all time points (Fig. 4A). At Day 180, the LSM difference (95% CI) between cryoneurolysis recipients and RFA recipients was -4.8 (-11.4, 1.9; P = 0.15), and at Day 360, it was -10.5 (-16.6, -4.4; P = 0.002). At Days 120, 150, 240, 300, 330, and 360, adjusted LSM ODI scores were significantly lower in cryoneurolysis recipients than in RFA recipients ($P \leq 0.03$; Suppl. Table 2). The mean percent decrease in ODI scores from the baseline was greater in cryoneurolysis recipients than in RFA recipients at Day 180 (-14.6% vs. -10.5%; P = 0.82; Fig. 4B) and was greatest at Day 360 (-21.7% vs. -4.0%; P = 0.42). More cryoneurolysis-treated patients than RFA-treated patients had "no disability" at Days 60, 120, 150, 180, 240, 270, 300, 330, and 360 (Table 2).

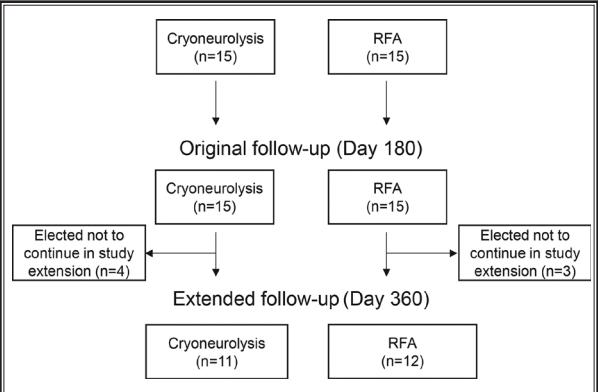

Fig. 2. *Flow diagram of patients.*
RFA, radiofrequency ablation.

PGIC and Patient Satisfaction with Pain Management Outcomes

Adjusted LSM PGIC scores for both groups are shown in Fig. 5A. The LSM difference (95% CI) between cryoneurolysis and RFA at Day 180 was -1.0 (-2.5, 0.6; P = 0.2) and at Day 360 was -2.6 (-4.2, -1.1; P = 0.002). Cryoneurolysis was associated with significant improvements in adjusted LSM PGIC scores compared with RFA at Days 120, 330, and 360 ($P \leq 0.01$; Suppl. Table 3). From Day 240 through Day 360, more patients were satisfied with pain management after cryoneurolysis than after RFA (Fig. 5B). At Day 180, most patients in both groups expressed a belief that the treatment procedure they received was beneficial (73% [11/15] in the cryoneurolysis group; 67% [10/15] in the RFA group). Additionally, at Day 180, a simi-

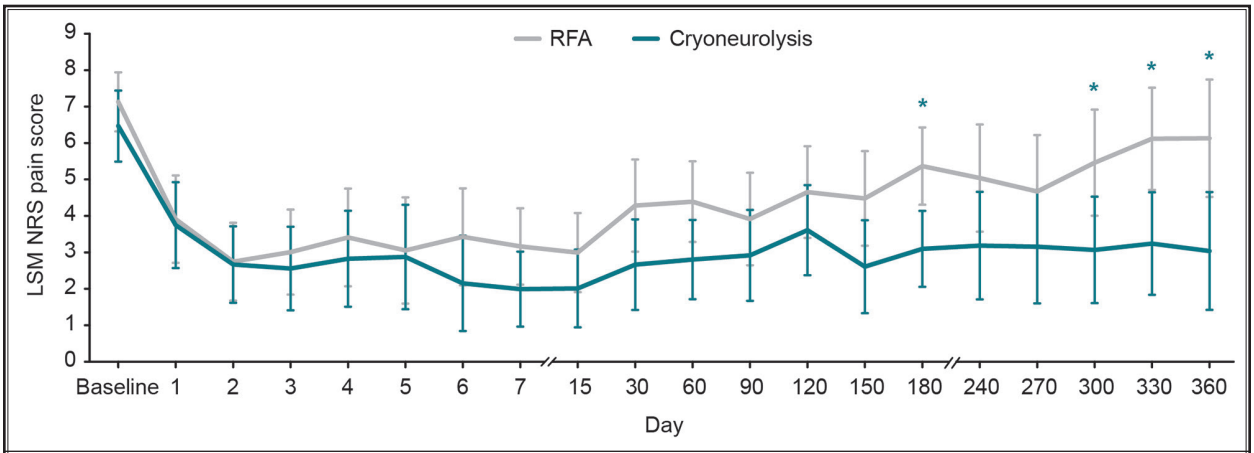

Fig. 3. *Adjusted LSM NRS scores of "average pain over the past 24 hours" through 360 days.*
*P < 0.05. Baseline mean was not adjusted for covariates, including baseline NRS, gender, and tobacco-use status. Data from Day 210 were excluded because the request to extend the study was under evaluation. Error bars are the 95% confidence interval.
NRS, numerical rating scale; LSM, least squares mean; RFA, radiofrequency ablation.

lar percentage of patients in both groups indicated willingness to undergo the same treatment procedure again (60% [9/15] in the cryoneurolysis group; 67% [10/15] in the RFA group).

Additional Spinal Injection

After Day 180, 54.5% of patients in the cryoneurolysis group did not undergo an additional spinal injection, in contrast with only 25% of patients in the RFA group (Table 3). One or more additional spinal injections (facet, epidural, spinal trigger point, or other) were required for 45.5% of the cryoneurolysis recipients and 75% of the RFA recipients.

Safety

No adverse device effects, serious adverse device effects, or SAEs were observed. Only one AE was reported in the study (a mild compression fracture in the cryoneurolysis group) and was considered unrelated to study treatment by the investigator.

Discussion

In this randomized pilot study, the first to follow patients for 12 months after cryoneurolysis with the iovera° system, patients who received cryoneurolysis for their CLBP had more significant improvements in pain, disability, and overall impression of treatment at Day 360 than did patients who received RFA. Improvements in pain observed in the cryoneurolysis group are notable because, unlike in the RFA group, steroids were not administered to the cryoneurolysis recipients, suggesting that cryoneurolysis may result in less overall pain than RFA. Patients who received cryoneurolysis were more satisfied with pain management at Day 360 than were those who received RFA, and more cryoneurolysis recipients than RFA recipients had "treatment success,"

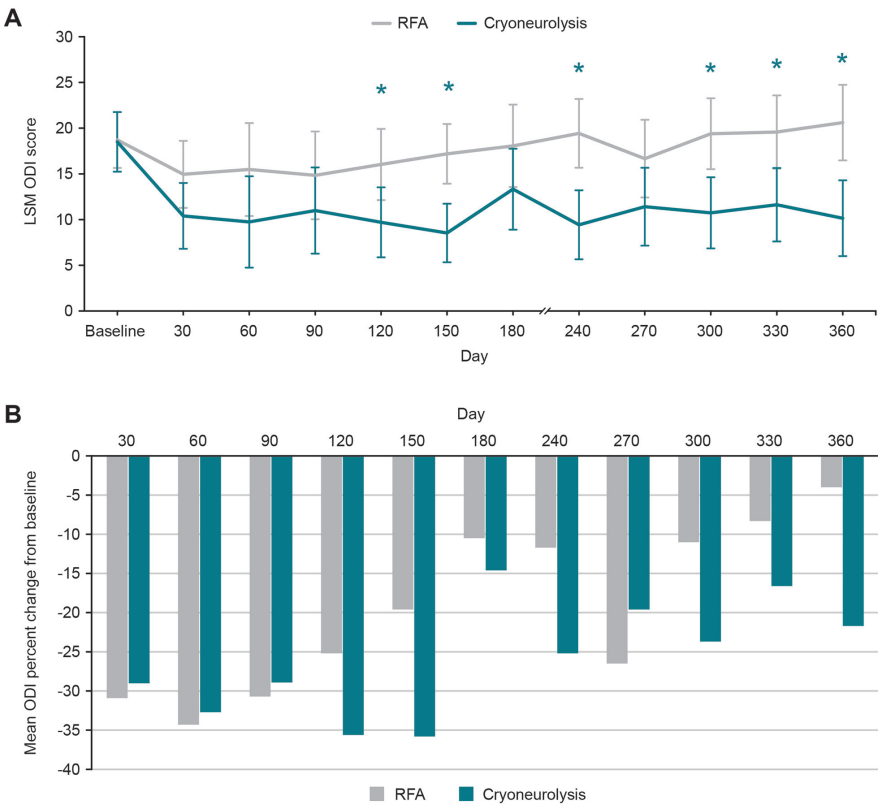

Fig. 4. *(A) Adjusted LSM ODI scores through 360 days. *P < 0.05. Baseline mean was not adjusted for covariates, including baseline NRS, gender, and tobacco-use status. Data from Day 210 were excluded because the request to extend the study was under evaluation. Error bars are the 95% confidence interval. (B) Mean percent change in ODI from baseline. Data from Day 210 were excluded because the request to extend the study was under evaluation.*
NRS, numeric rating scale; LSM, least squares mean; ODI, Oswestry Disability Index; RFA, radiofrequency ablation.

as defined by reduction of pain to ≤ 50% of the pre-treatment level. No treatment-related AEs or adverse device effects were reported. More patients who received RFA required additional spinal injections after Day 180 than did those who received cryoneurolysis, suggesting that when compared to RFA, cryoneurolysis may reduce the need for additional treatments.

Table 2. *ODI over time.*

Time and Treatment	n	No Disability n (%)	Mild n (%)	Moderate n (%)	Severe n (%)n	Completely Disabled (%)
Baseline						
RFA	15	0	3 (20.0)	10 (66.7)	2 (13.3)	0
Cryoneurolysis	15	0	5 (33.3)	6 (40.0)	4 (26.7)	0
Day 30						
RFA	15	2 (13.3)	9 (60.0)	3 (20.0)	1 (6.7)	0
Cryoneurolysis	15	2 (13.3)	7 (46.7)	4 (26.7)	2 (13.3)	0
Day 60						
RFA	15	3 (20.0)	8 (53.3)	2 (13.3)	1 (6.7)	1 (6.7)
Cryoneurolysis	15	5 (33.3)	5 (33.3)	2 (13.3)	3 (20.0)	0
Day 90						
RFA	15	3 (20.0)	8 (53.3)	2 (13.3)	1 (6.7)	1 (6.7)
Cryoneurolysis	15	2 (13.3)	8 (53.3)	4 (26.7)	1 (6.7)	0
Day 120						
RFA	15	1 (6.7)	8 (53.3)	4 (26.7)	1 (6.7)	1 (6.7)
Cryoneurolysis	15	5 (33.3)	3 (20.0)	7 (46.7)	0	0
Day 150						
RFA	15	1 (6.7)	6 (40.0)	7 (46.7)	1 (6.7)	0
Cryoneurolysis	15	4 (26.7)	6 (40.0)	4 (26.7)	1 (6.7)	0
Day 180						
RFA	15	0	7 (46.7)	5 (33.3)	3 (20.0)	0
Cryoneurolysis	15	4 (26.7)	3 (20.0)	6 (40.0)	2 (13.3)	0
Day 240						
RFA	12	0	5 (41.7)	5 (41.7)	2 (16.7)	0
Cryoneurolysis	11	4 (36.4)	4 (36.4)	3 (27.3)	0	0
Day 270						
RFA	12	1 (8.3)	5 (41.7)	5 (41.7)	1 (8.3)	0
Cryoneurolysis	11	2 (18.2)	5 (45.5)	4 (36.4)	0	0
Day 300						
RFA	12	0	6 (50.0)	4 (33.3)	2 (16.7)	0
Cryoneurolysis	11	1 (9.1)	5 (45.5)	5 (45.5)	0	0
Day 330						
RFA	12	0	5 (41.7)	4 (33.3)	2 (16.7)	1 (8.3)
Cryoneurolysis	11	1 (9.1)	6 (54.5)	4 (36.4)	0	0
Day 360						
RFA	12	0	5 (41.7)	5 (41.7)	2 (16.7)	0
Cryoneurolysis	11	1 (9.1)	5 (45.5)	5 (45.5)	0	0

ODI, Oswestry Disability Index; RFA, radiofrequency ablation.

Cryoneurolysis has several potential benefits over RFA. As previously noted, the temperature of cryoneurolysis results in Wallerian degeneration and is thus the less ablative procedure, leaving the endoneurium, perineurium, and surrounding structures intact (15,16,18). Because the mechanism of cryoneurolysis preserved surrounding tissue and allowed nerve regrowth, the musculature of patients who received cryoneurolysis in this study might have remained functionally intact, with reinnervation of target muscles occurring even while pain was still reduced at the one-year follow-up (15,28). The clinical approach for cryoneurolysis is similar to that for RFA, which may support ready implementation in clinical practice, and the handheld device may further increase ease of use and handling.

To the authors' knowledge, prospective data comparing outcomes associated with cryoneurolysis to those associated with RFA for the treatment of CLBP are limited. Previous studies in which cryoneurolysis techniques were applied for CLBP used devices that employed carbon dioxide as the coolant for patient populations with lumbar facet syndrome, a type of CLBP (19,22-24). Carbon dioxide results in temperatures of -50°C to -79°C, whereas nitrous oxide, used in the current study, results in temperatures of -60°C to -88°C (15,19,23). One prospective study found that 62% of patients (31/50) who underwent cryoneurolysis experienced > 50% pain reduction at one year, and all patients at all postoperative visits had a significant reduction

low back pain (specifically, facet joint pain) and found no differences between the groups in pain intensity or functional status at any time up to 12 months after treatment (30). Notably, this study had broader selec-

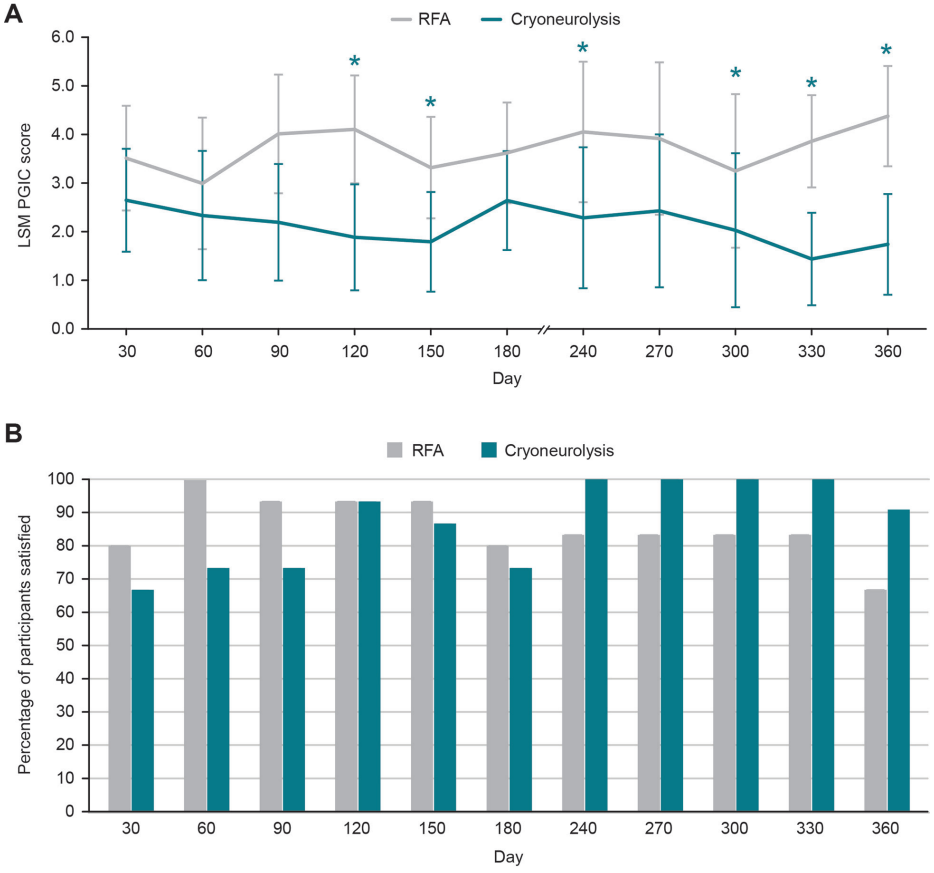

Fig. 5. *(A) Adjusted LSM PGIC score through 360 days. *P < 0.05. Data from Day 210 were excluded because the request to extend the study was under evaluation. Error bars are the 95% confidence interval. (B) Patient satisfaction with pain management through 360 days. Data from Day 210 were excluded because the request to extend the study was under evaluation.*
LSM, least squares mean; PGIC, Patient Global Impression of Change; RFA, radiofrequency ablation.

in VAS pain scores (22). Similar results were found in another prospective study in which cryoneurolysis resulted in 40% of patients (30/76) experiencing reduced pain at ≥ 12 months and all patients having reduced VAS scores through 6 months (24). Additionally, 56% of patients (43/76) who received more than one cryoneurolysis treatment experienced pain reduction for at least 12 months (24). A third prospective study found that cryoneurolysis resulted in a statistically significant improvement of ≥ 50% in low back pain for all patients (23). Finally, a retrospective study that measured outcomes over 4 years found that cryoneurolysis resulted in reduced pain at the final follow-up (mean, 1.7 years; range, 6-52 months) for patients with lumbar facet joint syndrome (29). A randomized controlled trial in Denmark compared cryoneurolysis (at a temperature of -80°C) to RFA with a placebo for the treatment of

Table 3. *Additional spinal injections after Day 180*[a].

	RFA (n = 12)	Cryoneurolysis (n = 11)
Additional spinal injection, n (%)	9 (75.0)	5 (45.5)
Lumbar spine, n	8	7
Epidural	2 (13.3)	1 (6.7)
Facet	2 (13.3)	6 (40.0)
Spinal trigger point	2 (13.3)	0
Other	2 (13.3)	0
Cervical, n	3	0
Facet	2 (13.3)	0
Spinal trigger point	1 (6.7)	0
Thoracic, n	1	0
Spinal trigger point	1 (6.7)	0

RFA, radiofrequency ablation.
[a]Some patients received more than one injection.

tion criteria (e.g., inclusion of patients who had prior surgery and patients taking opioids) and used a larger introducer needle for cryoneurolysis (14-gauge) than the current study (18-gauge) and required only one diagnostic nerve block, so that earlier study might have included patients who did not have true facet-mediated CLBP (30). More importantly, the protocol published before study completion suggested that the medial branch targets might not have been reached on the basis of cannular placement (31). Overall, the findings of the current pilot study are mostly consistent with previous evidence that cryoneurolysis can provide prolonged reductions in CLBP for at least a year.

Interestingly, consensus practice guidelines for lumbar facet joint pain recommend repeating RFA for pain relief up to twice a year for patients with a high rate of RFA success (≥ 80%), but these guidelines also note that the success rate decreases for consecutive procedures (6). Two of the studies described previously assessed the effect of repeat cryoneurolysis procedures on pain. In one of the prospective studies, the pain reduction after repeat cryoneurolysis treatment was similar to that observed for the first treatment; however, 11 of the 18 patients who underwent one or more repeat cryoneurolysis treatments did not experience pain reduction (24). Repeat cryoneurolysis for 22 patients in the retrospective study resulted in significantly lower ratings on the VAS at one day, 3 months, and the final follow-up at a mean of 1.7 years (29). Interestingly, 4 patients underwent a third cryoneurolysis treatment but experienced less of a benefit than after the first 2 treatments. Because cryoneurolysis produces sustained reductions in pain, repeat administration of cryoneurolysis may not be needed; however, more research is needed to confirm these findings (16,17,22-24).

Limitations

This study does have some limitations. Because this was a pilot study, the sample size was small and did not allow for formal hypothesis testing. Additionally, the study was not blinded; however, data on additional spinal injection requirements helped confirm patient experience. Notably, the 2 study administrators who followed up with patients in either group applied the same follow-up criteria within each group. The included patients also had relatively low body mass indexes because the tip of the cryoneurolysis device was short and could not extend through excess adipose tissue. A longer tip for the cryoneurolysis device used in the study received Food and Drug Administration 510k clearance in December 2024, which will make this treatment available to a broader range of patients (32). Although it cannot be ruled out that patients who received RFA or cryoneurolysis might have experienced residual effects of RFA that occurred at least 6 months before the current study, we believe this possibility was unlikely to be a confounder because the evidence for the long-term effectiveness of RFA is merely moderate (9). Additionally, patients in the RFA group received steroids after RFA treatment, although steroids to treat pain after RFA have only a low level of certainty, according to ASPN guidelines (6).

Conclusion

Overall, this pilot study of patients with long-standing CLBP demonstrated that cryoneurolysis resulted in sustained improvements in pain and disability for one year as well as a favorable safety profile, with data supporting that cryoneurolysis had advantages over RFA. A large multicenter trial is warranted to confirm these results and further investigate the effects of cryoneurolysis on CLBP.

Author Contributions

MGF, OB, KC, MD, and JS contributed substantially to the conception and design of the study and interpretation of the data. MGF and KC contributed substantially to the acquisition of the data. MC contributed substantially to the analysis of the data of the study. All authors reviewed the work critically, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Data Sharing Statement

To protect intellectual property, the data sets generated and/or analyzed during the current study are not publicly available, but they are available from the corresponding author on reasonable request.

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Suppl. Table 1. *Adjusted LSM NRS pain scores.**

	RFA	Cryoneurolysis	LSM Difference
30 days, n	15	15	
LSM NRS pain scores (95% CI) *P*-value	4.3 (3.0, 5.5) -	2.7 (1.4, 3.9) -	-1.5 (-3.4, 0.5) 0.13
60 days, n	15	15	
LSM NRS pain scores (95% CI) *P*-value	4.4 (3.3, 5.5) -	2.8 (1.7, 3.9) -	-1.5 (-3.1, 0.2) 0.08
90 days, n	15	15	
LSM NRS pain scores (95% CI) *P*-value	3.9 (2.6, 5.2) -	2.9 (1.7, 4.2) -	-0.7 (-2.4, 1.1) 0.46
120 days, n	15	15	
LSM NRS pain scores (95% CI) *P*-value	4.7 (3.4, 5.9) -	3.6 (2.4, 4.8) -	-0.9 (-2.7, 1.0) 0.36
150 days, n	15	15	
LSM NRS pain scores (95% CI) *P*-value	4.5 (3.2, 5.8) -	2.6 (1.3, 3.9) -	-1.7 (-3.6, 0.3) 0.09
180 days, n	15	15	
LSM NRS pain scores (95% CI) *P*-value	5.4 (4.3, 6.4) -	3.1 (2.1, 4.1) -	-2.1 (-3.6, -0.5) 0.01
240 days, n	12	11	
LSM NRS pain scores (95% CI) *P*-value	5.0 (3.6, 6.5) -	3.2 (1.7, 4.7) -	-1.6 (-3.6, 0.5) 0.12
270 days, n	12	11	
LSM NRS pain scores (95% CI) *P*-value	4.7 (3.1, 6.2) -	3.2 (1.6, 4.7) -	-1.3 (-3.6, 1.0) 0.24
300 days, n	12	11	
LSM NRS pain scores (95% CI) *P*-value	5.5 (4.0, 6.9) -	3.1 (1.6, 4.5) -	-2.5 (-4.7, -0.2) 0.03
330 days, n	12	11	
LSM NRS pain scores (95% CI) *P*-value	6.1 (4.7, 7.5) -	3.2 (1.8, 4.6) -	-2.9 (-5.1, -0.8) 0.01
360 days, n	12	11	
LSM NRS pain scores (95% CI) *P*-value	6.1 (4.5, 7.7) -	3.0 (1.4, 4.7) -	-2.7 (-4.7, -0.7) 0.01

*Adjusted for covariates including baseline NRS, gender, and tobacco-use status.
CI, confidence interval; LSM, least squares mean; NRS, numerical rating scale; RFA, radiofrequency ablation.

Suppl. Table 2. ***Adjusted LSM NRS ODI scores.****

	RFA	Cryoneurolysis	LSM Difference
30 days, n	15	15	
LSM ODI scores (95% CI) *P*-value	14.9 (11.2, 18.6) -	10.4 (6.8, 14.0) -	-4.6 (-10.0, 0.9) 0.10
60 days, n	15	15	
LSM ODI scores (95% CI) *P*-value	15.5 (10.4, 20.6) -	9.7 (4.7, 14.7) -	-5.7 (-13.2, 1.8) 0.13
90 days, n	15	15	
LSM ODI scores (95% CI) *P*-value	14.8 (10.0, 19.6) -	11.0 (6.3, 15.7) -	-3.9 (-10.9, 3.2) 0.27
120 days, n	15	15	
LSM ODI scores (95% CI) *P*-value	16.0 (12.1, 19.9) -	9.7 (5.9, 13.5) -	-6.3 (-12.1, -0.6) 0.03
150 days, n	15	15	
LSM ODI scores (95% CI) *P*-value	17.2 (13.9, 20.5) -	8.5 (5.3, 11.7) -	-8.7 (-13.5, -3.9) 0.001
180 days, n	15	15	
LSM ODI scores (95% CI) *P*-value	18.1 (13.6, 22.6) -	13.3 (8.9, 17.7) -	-4.8 (-11.4, 1.9) 0.15
240 days, n	12	11	
LSM ODI scores (95% CI) *P*-value	19.4 (15.7, 23.2) -	9.4 (5.7, 13.2) -	-10.0 (-15.6, -4.5) 0.001
270 days, n	12	11	
LSM ODI scores (95% CI) *P*-value	16.7 (12.4, 20.9) -	11.4 (7.1, 15.7) -	-5.3 (-11.5, 1.0) 0.10
300 days, n	12	11	
LSM ODI scores (95% CI) *P*-value	19.4 (15.5, 23.3) -	10.7 (6.8, 14.6) -	-8.7 (-14.4, -2.9) 0.005
330 days, n	12	11	
LSM ODI scores (95% CI) *P*-value	19.6 (15.6, 23.6) -	11.6 (7.6, 15.6) -	-8.0 (-13.9, -2.0) 0.01
360 days, n	12	11	
LSM ODI scores (95% CI) *P*-value	20.6 (16.5, 24.7) -	10.1 (6.0, 14.3) -	-10.5 (-16.6, -4.4) 0.002

*Adjusted for covariates including baseline NRS, gender, and tobacco-use status.
CI, confidence interval; LSM, least squares mean; NRS, numerical rating scale; ODI, Oswestry Disability Index; RFA, radiofrequency ablation.

Suppl. Table 3. ***Adjusted LSM NRS PGIC scores.****

	RFA	Cryoneurolysis	LSM Difference
30 days, n	15	15	
LSM PGIC scores (95% CI) *P*-value	3.5 (2.4, 4.6) -	2.6 (1.6, 3.7) -	-0.9 (-2.5, 0.7) 0.27
60 days, n	15	15	
LSM PGIC scores (95% CI) *P*-value	2.9 (1.6, 4.3) -	2.3 (1.0, 3.7) -	-0.7 (-2.7, 1.3) 0.50
90 days, n	15	15	
LSM PGIC scores (95% CI) *P*-value	4.0 (2.8, 5.2) -	2.2 (1.0, 3.4) -	-1.8 (-3.6, -0.02) 0.05
120 days, n	15	15	
LSM PGIC scores (95% CI) *P*-value	4.1 (3.0, 5.2) -	1.9 (0.8, 3.0) -	-2.2 (-3.9, -0.6) 0.01
150 days, n	15	15	
LSM PGIC scores (95% CI) *P*-value	3.3 (2.3, 4.4) -	1.8 (0.8, 2.8) -	-1.5 (-3.1, 0.01) 0.05
180 days, n	15	15	
LSM PGIC scores (95% CI) *P*-value	3.6 (2.6, 4.7) -	2.6 (1.6, 3.7) -	-1.0 (-2.5, 0.6) 0.20
240 days, n	12	11	
LSM PGIC scores (95% CI) *P*-value	4.1 (2.6, 5.5) -	2.3 (0.8, 3.7) -	-1.8 (-3.9, 0.4) 0.10
270 days, n	12	11	
LSM PGIC scores (95% CI) *P*-value	3.9 (2.3, 5.5) -	2.4 (0.9, 4.0) -	-1.5 (-3.8, 0.83) 0.19
300 days, n	12	11	
LSM PGIC scores (95% CI) *P*-value	3.2 (1.7, 4.8) -	2.0 (0.4, 3.6) -	-1.2 (-3.6, 1.1) 0.29
330 days, n	12	11	
LSM PGIC scores (95% CI) *P*-value	3.9 (2.9, 4.8) -	1.4 (0.5, 2.4) -	-2.4 (-3.8, -1.0) 0.002
360 days, n	12	11	
LSM PGIC scores (95% CI) *P*-value	4.4 (3.3, 5.4) -	1.7 (0.7, 2.8) -	-2.6 (-4.2, -1.1) 0.002

*Adjusted for covariates, including baseline NRS, gender, and tobacco-use status.
CI, confidence interval; LSM, least squares mean; NRS, numerical rating scale; PGIC, Patient Global Impression of Change; RFA, radiofrequency ablation.