A commentary by Gregory B. Maletis, MD, is linked to the online version of this article at jbjs.org.

Cooled Radiofrequency Ablation Compared with a Single Injection of Hyaluronic Acid for Chronic Knee Pain

A Multicenter, Randomized Clinical Trial Demonstrating Greater Efficacy and Equivalent Safety for Cooled Radiofrequency Ablation

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Background: Knee osteoarthritis is a painful and sometimes debilitating disease that often affects patients for years. Current treatments include short-lasting and often repetitive nonsurgical options, followed by surgical intervention for appropriate candidates. Cooled radiofrequency ablation (CRFA) is a minimally invasive procedure for the treatment of pain related to knee osteoarthritis. This trial compared the efficacy and safety of CRFA with those of a single hyaluronic acid (HA) injection.

Methods: Two hundred and sixty subjects with knee osteoarthritis pain that was inadequately responsive to prior nonoperative modalities were screened for enrollment in this multicenter, randomized trial. One hundred and eighty-two subjects who met the inclusion criteria underwent diagnostic block injections and those with a minimum of 50% pain relief were randomized to receive either CRFA on 4 genicular nerves or a single HA injection. One hundred and seventy-five subjects were treated (88 with CRFA and 87 with HA). Evaluations for pain (Numeric Rating Scale [NRS]), function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]), quality of life (Global Perceived Effect [GPE] score and EuroQol-5 Dimensions-5 Level [EQ-5D-5L] questionnaire), and safety were performed at 1, 3, and 6 months after treatment.

Results: Demographic characteristics did not differ significantly between the 2 study groups. A total of 158 subjects (76 in the CRFA group and 82 in the HA group) completed the 6-month post-treatment follow-up. In the CRFA group, 71% of the subjects had ≥50% reduction in the NRS pain score (primary end point) compared with 38% in the HA group ($p < 0.0001$). At 6 months, the mean NRS score reduction was 4.1 ± 2.2 for the CRFA group compared with 2.5 ± 2.5 for the HA group ($p < 0.0001$). The mean WOMAC score improvement at 6 months from baseline was 48.2% in the CRFA group and 22.6% in the HA group ($p < 0.0001$). At 6 months, 72% of the subjects in the CRFA group reported improvement in the GPE score compared with 40% in the HA group ($p < 0.0001$).

Conclusions: CRFA-treated subjects demonstrated a significant improvement in pain relief and overall function compared with subjects treated with a single injection of HA. No serious adverse events related to either procedure were noted, and the overall adverse-event profiles were similar.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

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A **data-sharing statement** is provided with the online version of the article (http://links.lww.com/JBJS/F978).

Knee osteoarthritis is the most common cause of chronic knee pain, affecting an estimated 14 million people in the United States[1]. Total knee replacement is the terminal procedure for late-stage knee osteoarthritis. Many patients (up to 25%) are not well-suited for surgery due to age, health, or other factors[2,3]. The nonoperative management of knee osteoarthritis symptoms remains of considerable interest to the medical community. As the durability of total knee replacement is approximately 20 years, many surgeons delay surgery and manage symptoms with more conservative treatments.

Nonsurgical management of knee osteoarthritis includes weight loss, activity modification, and physical therapy. Other treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), oral opioids, and duloxetine, which can be associated with a number of adverse events[4-8]. Intra-articular corticosteroid injections can provide short-term pain relief, but repeated injections may cause cartilage damage[9-12]. Platelet-rich plasma injections are a more recent technique, but questions surrounding standardization and the lack of robust clinical evidence remain[13-16].

Viscosupplementation involves the injection of hyaluronic acid (HA), or its derivatives, into the affected knee to provide lubrication and shock absorption[17]. Studies have demonstrated modest effects through 26 weeks[18]. The U.S. Food and Drug Administration (FDA) recently brought into question the mechanism of action of viscosupplementation[19], and clinical practice guidelines for orthopaedic surgeons do not currently recommend HA for the treatment of knee osteoarthritis pain[20].

Cooled radiofrequency ablation (CRFA) is the targeted thermal damage of nerve structures to interrupt the transmission of pain signals. Pain is believed to be attenuated while the nerve structure is restored[21]. Previous studies have

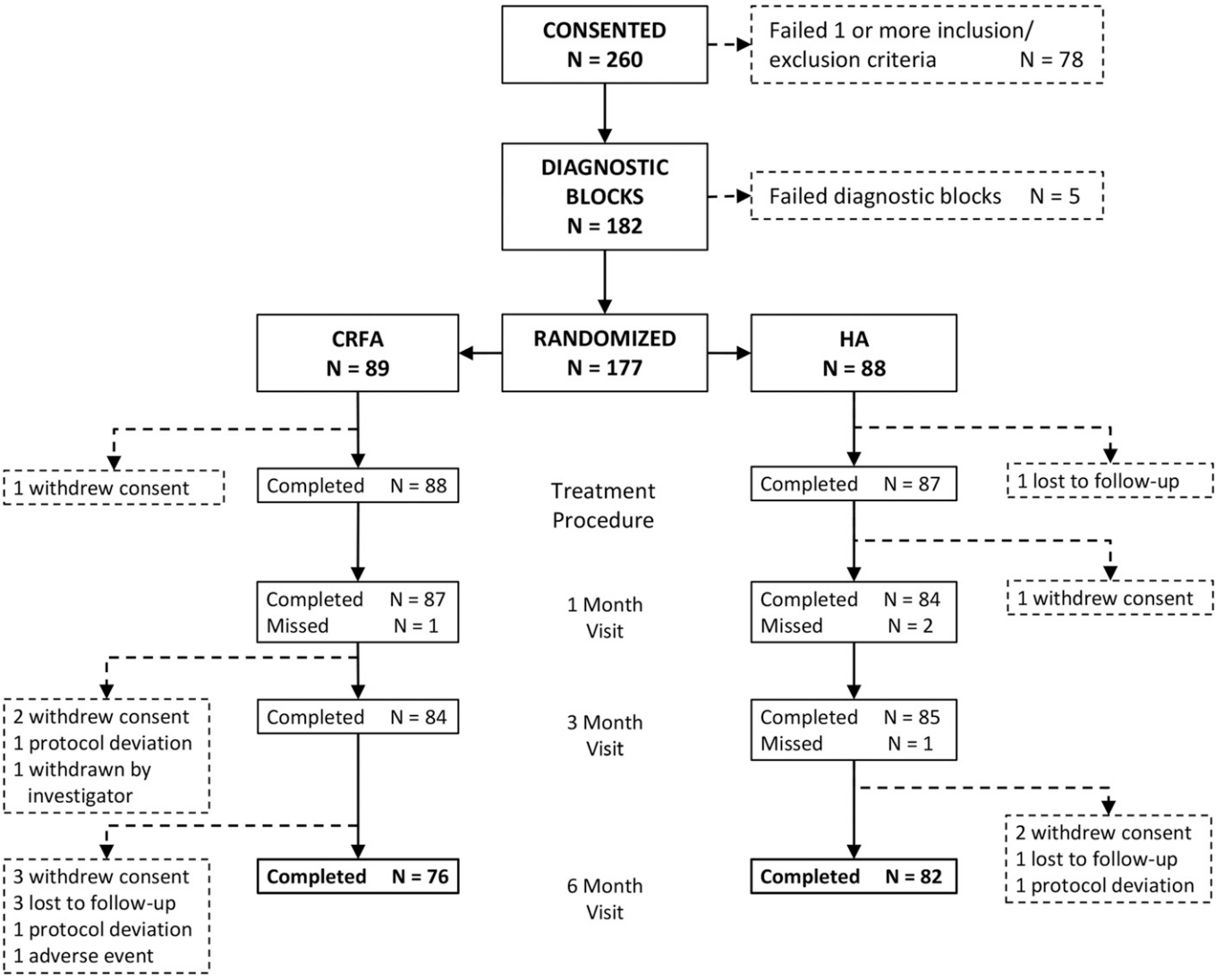

Fig. 1

CONSORT (Consolidated Standards of Reporting Trials) diagram depicting disposition of study participants.

TABLE I Breakdown of Subjects per Clinical Site

Investigational Site	No. of Patients							
			Randomized			Followed 6 Mo		
	Consented	Excluded when Screened	CRFA	HA	Total	CRFA	HA	Total
Institute for Orthopedic Research and Innovation	78	37	21	20	41	17	20	37
University Orthopedics Center Altoona	47	8	20	19	39	20	18	38
University Orthopedics Center State College	43	17	13	13	26	11	11	22
Virginia iSpine Physicians, PC	26	6	10	10	20	9	9	18
Mayo Clinic	5	1	2	2	4	2	1	3
PCPMG Clinical Research Unit, LLC	12	5	3	4	7	3	4	7
University of Pennsylvania	3	2	1	0	1	0	0	0
University of Virginia School of Medicine	22	3	9	10	19	8	10	18
Ochsner Clinic Foundation	14	4	5	5	10	2	4	6
Clinical Investigations, LLC	10	0	5	5	10	4	5	9
Total	260	83	89	88	177	76	82	158

demonstrated the efficacy of CRFA in managing knee osteoarthritis pain[22-28]. The durability of CRFA for relieving knee osteoarthritis pain is at least 6 months for the majority of subjects[22], with some trials demonstrating 12-month durability[23].

In light of the ongoing opioid epidemic, journal editorials have recently called for the development of effective non-opioid interventions[29]. Clinical literature has previously compared the efficacy of radiofrequency ablation to other nonoperative modalities, including placebos and corticosteroid injections[22,23,30]. There is a current gap in the understanding of the efficacy of CRFA compared with HA. While HA is not currently recommended by certain medical organizations, such as the American Academy of Orthopaedic Surgeons (AAOS)[20], it is within clinical guidelines established by other groups such as the Osteoarthritis Research Society International (OARSI)[31] and is currently used in clinical practice for varying grades of knee osteoarthritis. The purpose of this study was to conduct the first randomized, controlled trial to test the safety and efficacy of CRFA compared with injected HA for the management of knee pain in subjects with radiographically confirmed osteoarthritis.

Materials and Methods

The study protocol, informed-consent forms, subject recruitment materials, and study protocol amendments were approved by each center's institutional review board. All subjects provided informed consent prior to the initiation of screening activities. This trial was registered in ClinicalTrials.gov (NCT03381248) prior to initiation.

Study Subjects

All subjects presenting with signs and symptoms of knee osteoarthritis were considered for the trial. Full descriptions of inclusion and exclusion study criteria are shown in the Appendix. Study investigators determined the diagnosis of knee osteoarthritis for each trial candidate according to their medical history, presentation, physical examination, and radiographic confirmation of grade-2 (mild), 3 (moderate), or 4 (severe) osteoarthritis[32] within the previous 6 months in the affected (index) knee to be treated. Subjects with a positive response (≥50% reduction in pain) to a diagnostic nerve block were eligible to continue in the trial. Although subjects with bilateral knee osteoarthritis were not excluded, only 1 knee was screened and enrolled as the knee to be treated (i.e., the index knee).

Study Design

This randomized, multicenter study primarily compared the extent of osteoarthritis-related knee pain relief between subjects who underwent radiofrequency lesioning (COOLIEF* CRFA; Avanos Medical) of the genicular nerves, which are extracapsular sensory nerves of the knee joint[30,33], and subjects who received a single intra-articular HA injection (Synvisc-One [hylan G-F 20]; Sanofi). Study subjects received CRFA or an HA injection in a 1:1 randomization scheme, with post-treatment data collection at 1, 3, and 6 months. Six months was chosen as the duration of follow-up as that is the expected duration of medical improvement following HA injection for chronic knee pain[18]. Knee pain, function, overall subject impressions of treatment, quality of life, pain medication use, and adverse events were compared between the CRFA and HA treatment cohorts. The general knee condition determined through a physical examination performed by each designated medical professional was also recorded. At screening, this was intended to identify pathological conditions that could preclude osteoarthritis as a primary source of pain. As physical examinations of subjects with knee osteoarthritis can be painful, certain tests (e.g., the McMurray test) were performed with discretion and only

TABLE II Baseline Demographics

	CRFA	HA
No. of subjects	89	88
Age at consent		
Mean (SD) *(yr)*	63.3 (10.7)	63.1 (9.7)
Min., max. *(yr)*	37.8, 84.3	45.0, 90.8
P value (difference between groups)*	0.8954	
Sex		
Female *(no. [%])*	52 (58)	54 (61)
Male *(no. [%])*	37 (42)	34 (39)
P value (difference between groups)†	0.6902	
Prior index knee surgery *(no. [%])*		
Anterior cruciate ligament	4 (4)	2 (2)
Fracture	0 (0)	2 (2)
Meniscal injury	4 (4)	2 (2)
Body mass index		
Mean (SD) *(kg/m^2)*	32.2 (5.2)	30.5 (5.0)
Min., max. *(kg/m^2)*	20.4, 41.3	18.8, 39.9
P value (difference between groups)*	0.0260	
Duration of pain		
Mean (SD) *(mo)*	90.0 (87.5)	106.0 (124.4)
Min., max. *(mo)*	6.2, 439.9	6.0, 524.5
P value (difference between groups)*	0.3252	
Radiographic osteoarthritis grade in index knee *(no. [%])*		
1: None	0 (0.0)	0 (0.0)
2: Mild	15 (17)	24 (27)
3: Moderate	37 (42)	32 (36)
4: Severe	37 (42)	32 (36)
P value (difference between groups)‡	0.2001	
Decrease in NRS score after diagnostic block		
Mean (SD) *(%)*	91.3 (13.7)	92.5 (12.6)
Min., max. *(%)*	50.0, 100.0	57.1, 100.0
Difference between means: CRFA − HA (95% CI) *(%)*	−1.2 (−5.1, 2.7)	
P value (difference between groups)§	0.5571	

*T test for 2 independent means. †Chi-square test for proportions. ‡Wilcoxon/Wilcoxon-Mann-Whitney test for location. §Wilcoxon rank sum test for 2 independent samples.

when there was suspicion of a pathological entity other than osteoarthritis.

Diagnostic Block and Randomization

Subjects underwent fluoroscopically guided blockade of 4 target genicular nerves according to previously published procedures[22,33]. Diagnostic blocks were performed by the same investigator who subsequently performed either the HA or the CRFA treatment. A subject was deemed a positive responder if she/he experienced a ≥50% decrease in pain score on the Numeric Rating Scale (NRS) relative to baseline within 15 minutes after the injection of an anesthetic (preferably Marcaine [bupivacaine] 0.5% or a similar agent). Following a positive response, subjects were randomized to 1 of the 2 cohorts. Pain scores were reported using the NRS. The mean pain scores (and standard deviation [SD]) on the day of the diagnostic block were 6.5 ± 1.3 in the CRFA cohort and 6.5 ± 1.4 in the HA cohort. The mean pain scores following the diagnostic block were 0.6 ± 1.0 and 0.5 ± 0.8, respectively. The study procedures (CRFA or HA injection) were carried out within 30 days after randomization.

CRFA

Subjects randomized to the CRFA group underwent genicular ablation with previously published methods[22]. The 4 nerve targets for ablation were identified in accordance with previously published work[33]. Details of the procedural techniques are available in the Appendix.

Intra-Articular HA Injection

Synvisc-One was administered as a single intra-articular dose (6 mL), per the product's instructions for use. The preferred approach for injection was suprapatellar, unless there were anatomic limitations, in accordance with labeling. If necessary, an 18- to 20-gauge needle was used to remove synovial fluid or effusion before injection. Subjects were encouraged to refrain from strenuous activity for 48 hours.

Study Outcomes

The primary efficacy end point was the proportion of subjects ("responders") whose knee pain was reduced by ≥50% from baseline to 6 months after treatment. The 11-point NRS, ranging from 0 (no pain) to 10 (worst pain), was used to describe the amount of index knee pain at all study time points[34]. Other end points included knee pain, function, and stiffness as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[35], subjects' perception of treatment effect as reflected by the Global Perceived Effect (GPE) score[36], and the EuroQol-5 Dimensions-5 Level (EQ-5D-5L) health-related quality of life questionnaire[37]. Assessments of these study end points were made at baseline (except GPE) and at 1, 3, and 6 months following treatment. Outcome data were captured according to subjects' impressions during the week preceding data collection at each study

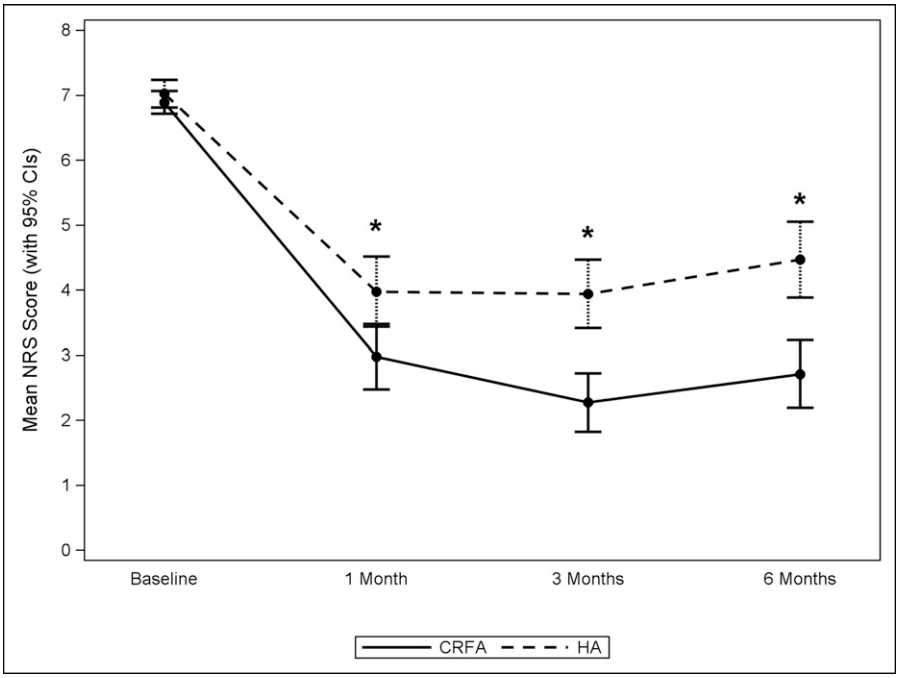

Fig. 2

Mean pain scores (NRS) and 95% confidence intervals (CIs) (bars) in the CRFA and HA cohorts with time. *Denotes a significant difference ($p \leq 0.05$) in means between groups at the indicated time point.

visit. In addition, demographic data, medical history, and concomitant medications were summarized. All subjects were evaluated for adverse events and serious adverse events at each visit.

Data Analysis

Data management, study site monitoring, and statistical services were performed by a third party independent of the study sponsor (Avanos Medical). Full details of the data analysis are available in the Appendix.

Results

Disposition of Study Participants

Of the 260 subjects screened, 83 did not meet inclusion criteria, including 5 subjects for whom the diagnostic blocks had failed. One hundred and seventy-seven subjects were randomized to study cohorts (CRFA: 89; HA: 88) (Fig. 1). One hundred and seventy-five (CRFA: 88; HA: 87) proceeded to treatment, whereas 2 did not due to withdrawal (1) or being lost to follow-up (1). At 1 and 3 months after treatment, 171 and 169 subjects remained in the study, respectively, whereas at 6 months, 158 subjects (CRFA: 76; HA: 82) were evaluated for study outcomes. A breakdown of subjects per clinical site is shown in Table I. Detailed demographic data are shown in Table II.

Primary Outcome: Knee Pain

The mean NRS scores indicated that the knee pain was nearly equivalent in the 2 cohorts at baseline and significantly reduced in the CRFA group compared with the HA group at 1 month ($p = 0.0085$), 3 months ($p < 0.0001$), and 6 months (mean NRS score reduction, 4.1 ± 2.2 compared with 2.5 ± 2.5, respectively; $p < 0.0001$) (Fig. 2). Furthermore, at 6 months, 71% of the CRFA users reported a ≥50% decrease in pain compared with 38% in the HA group ($p < 0.0001$).

General Knee Condition Following Study Interventions

The general condition of the knees—based on the mean total WOMAC scores and WOMAC pain, function, and stiffness subcategories—did not significantly differ between groups at baseline (Table III). At all but one of the follow-up time points, subjects who underwent CRFA had significantly better relief of knee pain and stiffness and enhanced knee function compared with those treated with HA. The mean WOMAC score improvement at 6 months from baseline was 48.2% in the CRFA group and 22.6% in the HA group ($p < 0.0001$). On physical examination 6 months following treatment, significantly fewer subjects in the CRFA cohort reported tenderness ($p < 0.0001$) and abnormal gait ($p = 0.0017$), whereas the proportions of all other knee examination findings were nearly equivalent in the 2 groups (see Appendix).

General Health of Subjects

Using 2 different self-completed tools to assess well-being (GPE and EQ-5D-5L), subjects who received CRFA reported being in significantly better general health than those who received an HA injection (Table IV). Significantly greater proportions of subjects reported their condition as "improved" on the GPE questionnaire at all follow-up time points in the CRFA cohort

TABLE III WOMAC Results Through 6 Months

	Baseline		1 Month		3 Months		6 Months	
	CRFA	HA	CRFA	HA	CRFA	HA	CRFA	HA
WOMAC total score								
No.	88	88	87	84	84	85	76	82
Mean	66.1	67.7	36.6	44.4	32.2	47.2	33.6	53.6
SD	13.2	13.3	23.1	21.4	23.1	22.1	22.9	22.9
Min.	28.1	38.5	0.0	7.3	0.0	0.0	0.0	2.1
Max.	92.7	97.9	100.0	92.7	79.2	92.7	89.6	96.9
Difference between means: CRFA − HA (95% CI)	−1.7 (−5.6, 2.3)		−7.8 (−14.5, −1.0)		−15.0 (−21.9, −8.1)		−19.9 (−27.1, −12.7)	
P value (difference between groups)*	0.4051		0.0239		<0.0001		<0.0001	
WOMAC pain score								
No.	89	88	87	84	84	85	76	82
Mean	67.8	68.6	37.1	44.8	32.8	47.6	35.9	53.3
SD	12.4	13.3	23.5	22.3	22.8	22.0	23.5	23.6
Min.	40.0	40.0	0.0	0.0	0.0	0.0	0.0	0.0
Max.	95.0	100.0	100.0	90.0	80.0	100.0	100.0	100.0
Difference between means: CRFA − HA (95% CI)	−0.9 (−4.7, 3.0)		−7.7 (−14.6, −0.8)		−14.8 (−21.6, −8.0)		−17.5 (−24.9, −10.1)	
P value (difference between groups)*	0.6585		0.0297		<0.0001		<0.0001	
WOMAC physical function score								
No.	88	88	87	84	84	85	76	82
Mean	64.6	66.8	35.4	43.4	30.8	46.1	32.3	53.0
SD	14.4	14.7	23.4	22.2	23.4	22.8	23.5	23.2
Min.	20.6	35.3	0.0	1.5	0.0	0.0	0.0	0.0
Max.	92.6	97.1	100.0	92.6	82.4	92.6	94.1	95.6
Difference between means: CRFA − HA (95% CI)	−2.1 (−6.5, 2.2)		−7.9 (−14.8, −1.0)		−15.3 (−22.3, −8.3)		−20.7 (−28.0, −13.4)	
P value (difference between groups)*	0.3294		0.0245		<0.0001		<0.0001	
WOMAC stiffness score								
No.	89	88	87	84	84	85	76	82
Mean	73.9	73.7	45.0	51.8	42.3	55.6	39.5	59.1
SD	21.9	17.8	28.6	25.1	30.6	24.7	26.9	26.1
Min.	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0
Max.	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Difference between means: CRFA − HA (95% CI)	0.2 (−5.8, 6.1)		−6.8 (−15.0, 1.3)		−13.3 (−21.8, −4.9)		−19.7 (−28.0, −11.3)	
P value (difference between groups)*	0.9590		0.1001		0.0022		<0.0001	

*T test for 2 independent means.

compared with the HA cohort. Moreover, subjects' responses to the EQ-5D-5L health-related quality of life questionnaire suggested that those in the CRFA cohort had a significantly improved overall health status compared with those in the HA cohort for up to 6 months following treatment (Table IV). Whereas the mean change from baseline in the EQ-5D-5L

TABLE IV Patients' General Health

	Baseline		1 Month		3 Months		6 Months	
	CRFA (N = 88)	HA (N = 86)	CRFA (N = 87)	HA (N = 84)	CRFA (N = 84)	HA (N = 85)	CRFA (N = 76)	HA (N = 82)
GPE score *(no. [%])*								
1: Worst ever			0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
2: Much worse			1 (1)	2 (2)	0 (0)	2 (2)	0 (0)	2 (2)
3: Worse			5 (6)	4 (5)	4 (5)	16 (19)	2 (3)	24 (29)
4: Not improved but not worse			12 (14)	26 (31)	13 (15)	24 (28)	18 (24)	22 (27)
5: Improved			27 (31)	30 (36)	21 (25)	22 (26)	24 (32)	16 (20)
6: Much improved			34 (39)	22 (26)	37 (44)	19 (22)	25 (33)	14 (17)
7: Best ever			8 (9)	0 (0)	8 (10)	2 (2)	6 (8)	3 (4)
P value (difference between groups)*			0.0010		<0.0001		<0.0001	
Distribution of GPE scores *(no. [%])*								
Not improved/worse			18 (21)	32 (38)	18 (21)	42 (49)	21 (28)	49 (60)
Improved			69 (79)	52 (62)	66 (79)	43 (51)	55 (72)	33 (40)
P value (difference between groups)†			0.0124		0.0001		<0.0001	
EQ-5D-5L index score								
Mean	0.67	0.66	0.79	0.76	0.82§	0.75	0.80	0.72
SD	0.12	0.13	0.10	0.11	0.10	0.12	0.11	0.13
Min.	0.29	0.30	0.50	0.43	0.56	0.34	0.43	0.40
Max.	0.83	0.83	1.00	1.00	1.00	1.00	1.00	1.00
Difference between means: CRFA − HA (95% CI)	0.02 (−0.02, 0.05)		0.04 (0.00, 0.07)		0.07 (0.03, 0.10)		0.09 (0.05, 0.12)	
P value (difference between groups)‡	0.4123		0.0259		0.0002		<0.0001	

*Wilcoxon-Mann-Whitney test for location. †Chi-square test for 2 categorical variables. ‡T test for 2 independent means. §N = 83.

index score was 0.06 in the HA group at 6 months, it was 0.12 in the CRFA group (p = 0.0075).

Medication Usage

Only 8 subjects in the CRFA group and 7 in the HA group were taking opioid medications at baseline. No significant changes were observed from baseline to the 6-month follow-up in either group (see Appendix). However, subjects decreased their total daily dose of non-opioid medications after 6 months in the CRFA group, whereas the opposite effect was noted in the HA group (see Appendix).

Adverse Events

A total of 157 adverse events (CRFA: 94; HA: 63) were reporting during this study period (Table V). The majority (83%) of these events were deemed unrelated to either procedure. In the CRFA group, 18 adverse events (19%) were noted as having some relationship to treatment (the CRFA procedure) compared with 9 (14%) in the HA treatment group. In each group, there was 1 instance of pain during the procedure that prevented the completion of the procedure. There were no instances of a Charcot joint in either subject population.

Discussion

Nonoperative management of pain associated with knee osteoarthritis is of substantial interest to orthopaedic surgeons. Cost-effective non-opioid strategies are needed to address the pain and disability associated with knee osteoarthritis for patients who are not currently candidates for arthroplasty[29]. At the 6-month follow-up in this study, CRFA demonstrated superior efficacy with regard to pain relief, higher quality of life, and better knee function when compared with a single HA injection, with similar adverse events.

The results of this study pertaining to pain reduction closely mimic response rates in other studies of CRFA[22,25]. Davis et al. compared the efficacy and safety of CRFA with those of intra-articular corticosteroid injections[22]. At 6 months, 74.1% of their subjects who received CRFA had pain reduction of >50%. Bellini and Barbieri reported that subjects who received CRFA had a mean visual analog scale (VAS) pain score of 2.1 ± 0.5 at 6 months, compared with a mean baseline score of 8.0 ±

1.5[25]. A retrospective study demonstrated that 65% of 183 subjects who received CRFA experienced >50% pain relief over an average time period of 12.5 months[28].

Previous HA trials have defined a positive clinical outcome as a 30% to 40% decrease in pain from baseline to the 3-month time point[38]. In comparison, subjects who received CRFA in our trial experienced a 67.1% decrease in pain (as measured with the NRS) from baseline to the 3-month time point. A review of clinical trials of intra-articular corticosteroids identified VAS pain reductions of 1.3 to 3.3 on a 10-point scale, with an average reduction of 2.2, at 1 week after the injection[9]. In comparison, the subjects who received CRFA in our trial had a mean reduction of 4.1 at 6 months.

Our subjects who received CRFA had significantly improved mean WOMAC scores for pain, physical function, and stiffness compared with those who received HA. Bellini and Barbieri reported a mean reduction in the total WOMAC score of 21 ± 1.7 at 6 months after CRFA[25]. Another clinical trial comparing a single HA injection with a placebo demonstrated that subjects in the treatment arm had a 31.3% improvement in the WOMAC pain

TABLE V Distribution of All Adverse Events, by Relationship with Procedure, During 6-Month Follow-up

	Possible, Probable, Definite, or Unlikely Relationship				Unrelated Relationship			
	CRFA (N = 89 Subjects)		HA (N = 88 Subjects)		CRFA (N = 89 Subjects)		HA (N = 88 Subjects)	
	Events *(no.)*	Subjects *(no. [%])*	Events *(no.)*	Subjects *(no. [%])*	Events *(no.)*	Subjects *(no. [%])*	Events *(no.)*	Subjects *(no. [%])*
All adverse events	18	13 (15)	9	9 (10)	76	44 (49)	54	37 (42)
Blood/lymphatic	0	0 (0)	0	0 (0)	1	1 (1)	0	0 (0)
Infection	0	0 (0)	0	0 (0)	1	1 (1)	0	0 (0)
Cardiovascular	0	0 (0)	0	0 (0)	3	3 (3)	1	1 (1)
Endocrine/ metabolic	0	0 (0)	0	0 (0)	2	2 (2)	0	0 (0)
Gastrointestinal	0	0 (0)	0	0 (0)	2	1 (1)	4	4 (5)
Genitourinary	0	0 (0)	0	0 (0)	1	1 (1)	2	2 (2)
HEENT*	0	0 (0)	0	0 (0)	1	1 (1)	0	0 (0)
Musculoskeletal	17	12 (13)	8	8 (9)	50	36 (40)	34	27 (31)
Procedure	0	0 (0)	0	0 (0)	2	2 (2)	1	1 (1)
Pain	3	3 (3)	3	3 (3)	23	22 (25)	21	21 (24)
Post-procedure pain	9	7 (8)	3	3 (3)	0	0 (0)	0	0 (0)
New injury	0	0 (0)	0	0 (0)	14	10 (11)	11	5 (6)
Pes bursitis	0	0 (0)	0	0 (0)	3	3 (3)	1	1 (1)
Baker cyst	0	0 (0)	2	2 (2)	0	0 (0)	0	0 (0)
Numbness	2	2 (2)	0	0 (0)	1	1 (1)	0	0 (0)
Instability	0	0 (0)	0	0 (0)	4	4 (4)	0	0 (0)
Stiffness/ tightness	2	1 (1)	0	0 (0)	1	1 (1)	0	0 (0)
Bruising/ swelling	1	1 (1)	0	0 (0)	0	0 (0)	0	0 (0)
Other	0	0 (0)	0	0 (0)	2	2 (2)	0	0 (0)
Neurological	0	0 (0)	0	0 (0)	3	3 (3)	2	2 (2)
Respiratory	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (1)
Skin	1	1 (1)	0	0 (0)	1	1 (1)	1	1 (1)
Other	0	0 (0)	1	1 (1)	12	9 (10)	9	9 (10)
Procedure	0	0 (0)	0	0 (0)	1	1 (1)	1	1 (1)
Fall	0	0 (0)	0	0 (0)	9	8 (9)	7	7 (8)
Other	0	0 (0)	1	1 (1)	2	2 (2)	1	1 (1)

*HEENT = head, eyes, ears, nose, and throat.

score from baseline at week 26[18]. Our CRFA group experienced a 46.0% improvement in the WOMAC pain score from baseline to 6 months. Of note, a 12% to 18% improvement in the WOMAC pain score from baseline is the minimum clinically accepted improvement in patients with osteoarthritis[39].

Our subjects who received CRFA had greater improvement in the GPE score than the subjects who received HA. Importantly, the difference in the EQ-5D-5L score in the CRFA group exceeded the minimal clinically important difference of 0.074 for that score[40]. In a previous trial, Davis et al. reported that 91.4% of subjects who received CRFA had improved GPE scores after 6 months[22]. A previous trial using the Patient Global Assessment showed that 37% of subjects who received HA injection reported feeling "very well" or "well."[18]

Of particular interest, subjects in this study with grade-2 osteoarthritis responded better than those with grade 3, who responded better than those with grade 4, suggesting that CRFA should be considered early in the osteoarthritis treatment paradigm.

Our study did not address the long-term theoretical risks associated with CRFA of the knee, including the possibility of vascular insult leading to osteonecrosis or the potential of a Charcot-type response in the joint. These potential complications have not been seen in longer-term CRFA studies, however[22,23,25,28,41], and our subjects did not present with any early symptoms of these complications. We conclude that CRFA is unlikely to result in these types of complications when conducted by adequately trained and experienced practitioners.

Limitations of this study include the low number of subjects reporting opioid use prior to the procedure, making it difficult to measure any trends in opioid consumption following treatment. Additionally, the open-label nature of the trial allows the opportunity for bias. At the time of trial inception, the control product used in this trial was the most commonly used HA product. Other protocols can involve 3, 4, or 5 injections, spaced weeks apart. However, the single injection also allowed for a single time point for measuring outcomes and treatment consistency within the study. Additionally, there was a higher rate of attrition in the CRFA cohort compared with the HA cohort (15% versus 7%), which was not a significant difference ($p = 0.09$). There was a lack of subject and provider blinding as a result of the pragmatic study design, given the differences in administering injections and CRFA. There was also a lack of balance across enrolling sites as a result of the variability of timing of the completion of pre-study documentation. However, a formal screening log was maintained at each site and routinely monitored to ensure lack of bias in subject selection. Finally, this study was funded by the manufacturer of CRFA devices, presenting a potential conflict of interest.

Certain resources are required when using CRFA, which typically is administered in the hospital setting, whereas HA injection often occurs in the office setting. However, economic studies have determined that CRFA is a cost-effective procedure[42].

In conclusion, the findings of this randomized study showed that CRFA is superior to a single injection of HA for the management of osteoarthritic knee pain. The majority of subjects receiving CRFA can expect at least 6 months of pain relief. CRFA also resulted in improved outcomes related to overall function (WOMAC scores) and quality of life (GPE scores) as compared with HA. Adverse-event profiles were similar, with no serious adverse events related to either procedure.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/F977). ■

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