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Appendix

Cooled Radiofrequency Ablation Technique

Subjects randomized to CRFA were placed in a supine position on a fluoroscopy table with a pillow under the popliteal fossa to alleviate discomfort. The true anteroposterior fluoroscopic view of the tibiofemoral joint was obtained to show the tibiofemoral joint space with equal width interspaces on both sides. An appropriately-sized CRFA needle was placed overlying the affected knee joint, and using fluoroscopic guidance, the needle was advanced to a bony endpoint on the superolateral portion of the femoral condyle of the affected knee. A second needle was advanced to a bony endpoint on the superomedial portion of the femoral condyle, and a third needle was positioned to the bony endpoint at the inferomedial portion of the tibial condyle. The final needle was placed at the midline of the femur, about 2 centimeters (cm) cephalad of the upper patellar border. Lateral x-ray views were created to confirm appropriate location at 50% depth of the femur and tibia prior to lesioning.

Care was taken to avoid inserting the CRFA probe into the inferolateral area of the knee, so as to avoid the common peroneal nerve and thus the potential for foot drop. Motor stimulation was tested at 2.0 volts with no leg movement, while sensory stimulation was conducted at < 0.5 volts in all four locations with concordant pain reproduction. A mixture consisting of lidocaine (1% or 2% preferred) was then slowly injected. Next, CRFA of each of the four targeted genicular nerves was conducted with a probe set temperature of 60°C for 2 minutes and 30 seconds, which produces an average tissue temperature greater than 80°C.

Upon conclusion of CRFA, the needles were removed, the insertion sites were treated with appropriate closure materials, and each subject was allowed to properly recover prior to discharge home. Instillation of post-operative analgesic pain medication was permissible per institutional standard of care. Discharged subjects were provided with instructions for self-care, which included limiting strenuous activity for at least 48 hours post-procedure. Otherwise, no post-procedural rehabilitation protocol was prescribed.

Data Analysis

A non-inferiority approach based on response rate was used to calculate the sample size for this study, with "response" defined as ≥ 50% reduction in pain from baseline on the NRS scale. The upper bound of a 2-sided 95% CI was calculated for the rate difference between treatments (Standard minus Test). If the upper bound was less than (δ), then "non-inferiority" achieved for the test treatment relative to standard treatment, as described in the table below:

Success Rate of CRFA (based on 50% Pain Score Reduction in VAS)	Success Rate of Standard (Based on 30% Pain Score Reduction in VAS)	Non-Inferiority Margin (δ)	Sample Size 5% Level of Significance (2-sided) 90% Statistical Power
62%*	40%**	5%	134

***** = [18]Chevalier X, et al. Ann Rheum Dis. 2010 Jan;69(1):113-9.

** = [23]Davis T, et al. Regional Anesthesia & Pain Medicine. 2019 Feb;44(4):499-506.

Assuming an attrition rate of 20%, 168 subjects enrolled into the study will yield 134 completers.

The non-inferiority margin is set at 5% for the primary efficacy parameter expressed as proportion. The difference of proportions between treatment groups will be calculated and a two-sided 95% confidence interval will be constructed using Wald asymptotic confidence limits approach or exact binomial limits approach. If the upper bound is less than 0.05, then 'Non-inferiority' is established for the CRFA group relative to the HA injection group. If, in addition, the upper bound of the confidence interval is below zero, the CRFA group can be determined to be 'Superior' to the HA injection group.

Employing that for CRFA responder rate=62% and HA responder rate=40%, the total necessary sample size for superiority (δ=0) is 162 (81 per group). If 20% attrition is expected, then total enrollment should be (necc. sample size)/(1-attrition rate) = 162/0.8 ~ 203.

Continuous data were reported using descriptive statistics, and categorical data were summarized as counts and percentages. Results of study endpoints were accompanied by descriptions of the statistical tests used to compare study groups. The p-value to indicate significance for the superiority for NRS-measured primary outcome of knee pain (≥ 50% relief compared to baseline pain) was 0.025, while that of all other presented outcomes was 0.05.

Demographics

Participants in the CRFA and HA study groups were equivalent, with no statistically significant differences observed between cohorts with respect to mean age at consent, mean duration of OA knee pain and gender or ethnicity (Table II). Mean body mass index (BMI) was significantly higher in the CRFA group. The majority of subjects had OA grades 3 and 4 in each group. Diagnostic blocks produced similar mean reductions in pain (NRS scores) of approximately 90% in each group. At baseline, similar proportions of subjects in each study group had experienced prior index knee procedures, including arthroscopy (p = 0.27), steroid injection (p = 0.46), and HA injections (p = 0.38). Patients in each group had similar OA symptoms: effusion, tenderness, flexion contracture, mild laxity, pain with extension, decreased strength, abnormal gait, positive McMurray test, crepitus, pain with flexion, and limited range of motion.

Dates of Enrollment and Follow-up.

The first informed consent form (ICF) was signed December 4th, 2017. The last ICF was signed August 3rd, 2018. The first subject was enrolled on December 7th, 2017. The last patient was enrolled August 16th, 2018. The last 6-month follow-up occurred on February 7th, 2019.

Randomization

Randomization treatment assignments were prepared by the study statistician using a computerized randomization program, and were loaded into the electronic data management system being utilized in the study. Upon confirmation that a subject was eligible for

randomization, sites logged into the system to randomize the subject. Randomization was stratified by site and blocked using block sizes 2, 4 and 6.

Specific instructions were provided in the database training materials. The monitor confirmed that the randomization process was being appropriately followed and documentation was being maintained as appropriate. Any deviation from the randomization process was immediately reported to the sponsor and documented appropriately.

Subgroup Analysis

Subgroup analyses was performed and included, but not be limited to, gender, age, OA grade and opioid use will be provided on the primary effectiveness endpoint. These analyses were regarded as exploratory. Subgroup analyses mirrored those of corresponding endpoint analyses.

Weight was tracked throughout the course of the trial, as the authors note the importance of weight loss when managing knee OA. However, there were no statistical changes in weight in either cohort. Additionally, BMI was included as a potential predictor of outcomes in a logistic regression model and was not shown to be statistically significant ($p = 0.26$).

Demographics of Study Responders

Study responders were those subjects who experienced ≥50% pain relief, as indicated by correspondingly reduced NRS scores, at 6 months following treatment. Logistic regression analyses revealed that treatment with CRFA ($p < 0.0001$) or Grade 2 OA ($p = 0.0374$) were significant predictors of response in this investigation. Regarding the latter, responses to CRFA became progressively less as subject's baseline OA grade worsened. Subjects in the CRFA cohort were more likely to respond to this treatment if they were less than 55 years old, male, or non-diabetic.

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Study Population Selection Criteria

Inclusion Criteria	Exclusion Criteria
1. Age ≥ 21 years.	1. Evidence of inflammatory arthritis (for example, rheumatoid arthritis) or other systemic inflammatory condition (for example, gout, fibromyalgia) that could cause knee pain.
2. Able to understand the informed consent form and provide written informed consent and able to complete outcome measures.	2. Evidence of neuropathic pain affecting the index knee.
3. Chronic knee pain for longer than 6 months that interferes with functional activities (for example, ambulation, prolonged standing, etc.).	3. Previous or pending lower limb amputation.
4. Continued pain in the target knee despite at least 3 months of conservative treatments, including activity modification, home exercise, protective weight bearing, and/or analgesics (for example, acetaminophen or NSAIDs.	4. Intra-articular steroid injection into the index knee within 90 days from randomization.
5. Positive response (defined as a decrease in numeric pain scores of at least 50%) to a single genicular nerve block of the index knee.	5. Hyaluronic acid injection, PRP, stem cell, or arthroscopic debridement/lavage injection into the index knee within 180 days from randomization.
6. Pain on NRS ≥ 6 on an 11-point scale for the index knee.	6. Prior RF ablation of the genicular nerves of the index knee.
7. Radiologic confirmation of arthritis (x-ray/MRI/CT) of OA grade of 2 (mild), 3 (moderate) or 4 (severe) noted within 6 months for the index knee.	7. Prior partial, resurfacing, or total knee arthroplasty of the index knee (residual hardware).
8. An intra-articular hyaluronic acid injection is indicated as an appropriate treatment option.	8. Clinically significant ligamentous laxity of the index knee.
9. WOMAC Knee Score group at baseline of score of ≥ 2 (0 to 4 scale) on WOMAC question 1 (pain) and a mean score of ≥ 1.5 on all five questions of the WOMAC pain subscale.	9. Clinically significant valgus/varus deformities or evidence of pathology (other than osteoarthritis of knee) that materially affects gait or function of the knee or is the underlying cause of the knee pain and/or functional limitations.
10. Analgesics including membrane stabilizers such as Neurontin/gabapentin and antidepressants for pain such as Cymbalta/duloxetine must be clinically stable (defined as stable dosage for ≥ 6 weeks prior to the screening visit) and shall not change during the course of the study without approval of the investigator.	10. BMI > 40 kilograms/meter^2.
11. Agree to see one physician (study physician) for knee pain during the study period.	11. Extremely thin patients and those with minimal subcutaneous tissue thickness that would not accommodate a RF lesion of up to 14 mm in diameter to limit the risk of skin burns.
12. Willing to utilize double barrier contraceptive method if of child bearing potential.	12. Pending or active compensation claim, litigation or disability remuneration (secondary gain).
13. Willing to delay any surgical intervention for the index knee for the period of the study follow-up.	13. Pregnant, nursing or intent on becoming pregnant during the study period.
14. Willingness to provide informed consent and to comply with the requirements of this protocol for the full duration of the study.	14. Chronic pain associated with significant psychosocial dysfunction.
	15. Beck's Depression Index score of > 22 (indicates clinically depressed state).

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	16. Allergies to any of the medications to be used during the procedures, including known hypersensitivity (allergy) to hyaluronate preparations or allergies to avian or avian-derived products (including eggs, feathers, or poultry). 17. Active joint infection or systemic or localized infection at needle entry sites (subject may be considered for inclusion once infection is resolved). 18. History of uncontrolled coagulopathy, ongoing coagulation treatment that cannot be safely interrupted for procedure, or unexplained or uncontrollable bleeding that is uncorrectable. 19. Identifiable anatomical variability that would materially alter the procedure as described in the protocol. 20. Within the preceding 2 years, subject has suffered from active narcotic addiction, substance, or alcohol abuse. 21. Current prescribed opioid medications greater than 60 morphine equivalent daily opioid dose. 22. Uncontrolled immunosuppression (e.g. AIDS, cancer, diabetes, etc.). 23. Subject currently implanted with pacemaker, stimulator or defibrillator. 24. Participating in another clinical trial/investigation within 30 days prior to signing informed consent 25. Subject unwilling or unable to comply with follow up schedule or protocol requirements
NSAID = nonsteroidal anti-inflammatory drugs, NRS = numeric rating (pain) scale, MRI = magnetic resonance imaging, CT = computed tomography, WOMAC = Western Ontario & McMaster University Osteoarthritis Index, PRP = platelet-rich plasma, RF = radiofrequency, BMI = body mass index, mm = millimeters, AIDS = acquired immunodeficiency syndrome	

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Knee Examination Findings through 6 Months - Index Knee

	Baseline			6 Months		
Knee Examination Findings n/N (%)	**CRFA**	**HA**	**P-value***	**CRFA**	**HA**	**P-value***
Findings During the Knee Exam (not mutually exclusive)						
Effusion	18/89 (20.2)	26/88 (29.5)	0.1514	6/75 (8.0)	13/82 (15.9)	0.1318
Tenderness	74/89 (83.1)	77/88 (87.5)	0.4133	29/75 (38.7)	60/82 (73.2)	<0.0001
Flexion Contracture	4/89 (4.5)	2/88 (2.3)	0.4141	0/75 (0.0)	4/82 (4.9)	0.0527
Mild Laxity	6/89 (6.7)	9/88 (10.2)	0.4051	3/75 (4.0)	7/82 (8.5)	0.2450
Pain with Extension	27/89 (30.3)	20/88 (22.7)	0.2517	12/75 (16.0)	21/82 (25.6)	0.1399
Decreased Strength	8/89 (9.0)	12/88 (13.6)	0.3288	1/75 (1.3)	2/82 (2.4)	0.6132
Abnormal Gait	22/89 (24.7)	24/88 (27.3)	0.6985	3/75 (4.0)	17/82 (20.7)	0.0017
Positive McMurray Test	8/89 (9.0)	14/88 (15.9)	0.1629	2/75 (2.7)	3/82 (3.7)	0.7237
Crepitus	54/89 (60.7)	52/88 (59.1)	0.8299	33/75 (44.0)	44/82 (53.7)	0.2266
Pain with Flexion	27/89 (30.3)	39/88 (44.3)	0.0545	10/75 (13.3)	18/82 (22.0)	0.1588
Limited Range of Motion	23/89 (25.8)	28/88 (31.8)	0.3801	8/75 (10.7)	15/82 (18.3)	0.1771
Leg Length Discrepancy	0/89 (0.0)	4/88 (4.5)	0.0419	0/75 (0.0)	0/82 (0.0)	N/A

CRFA, cooled radiofrequency ablation; HA, hyaluronic acid; *Chi-square test for proportions; N/A, not applicable.

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Total Daily Dose of Morphine Equivalence for Subjects Taking Opioids

	Baseline		1 Month		3 Month		6 Month	
	CRFA	**HA**	**CRFA**	**HA**	**CRFA**	**HA**	**CRFA**	**HA**
Pain Medication Usage								
N	8	7	7	6	7	8	5	7
Mean	15.1	17.5	19.3	15.4	18.5	18.1	22.7	17.3
SD	11.3	15.5	13.0	17.6	13.0	14.4	18.0	12.1
Median	12.5	10.0	22.5	7.5	15.0	16.3	30.0	17.5
Minimum	1.7	5.0	1.7	5.0	2.5	5.0	3.3	3.3
Maximum	30.0	50.0	36.7	50.0	40.0	50.0	45.0	35.0
Difference between means (CRFA-HA) and 95% CI	-2.4 (-17.4, 12.6)		3.9 (-14.8, 22.6)		0.3 (-15.1, 15.8)		5.4 (-13.8, 24.6)	
P-value (difference between groups)	0.9074**		0.7195**		1.0000**		0.7427**	
Change from Baseline in Pain Medication Usage								
N	--	--	5	5	5	5	3	5
Mean	--	--	3.5	-1.0	1.3	0.0	14.2	-4.5
SD	--	--	19.9	2.2	18.1	3.5	12.3	9.1
Median	--	--	0.0	0.0	-5.8	0.0	20.0	-5.0
Minimum	--	--	-25.7	-5.0	-15.0	-5.0	0.0	-15.0
Maximum	--	--	26.7	0.0	30.0	5.0	22.5	10.0
Difference between means (CRFA-HA) and 95% CI	--	--	4.5 (-20.1, 29.2)		1.3 (-20.9, 23.6)		18.7 (0.3, 37.0)	
P-value (difference between groups)	--	--	0.4802**		0.6723**		0.0719**	
P-value (change from Baseline)	--	--	0.7500$^{\$\$}$	1.0000$^{\$\$}$	1.0000$^{\$\$}$	1.0000$^{\$\$}$	0.5000$^{\$\$}$	0.3750$^{\$\$}$

***Wilcoxon rank sum test for two independent samples, $^{\$\$}$Wilcoxon signed rank test for paired samples*

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Total Daily Dose of Non-Morphine Pain Medications for Subjects Taking Non-Opioids

	Baseline		1 Month		3 Month		6 Month	
	CRFA	**HA**	**CRFA**	**HA**	**CRFA**	**HA**	**CRFA**	**HA**
Non-Morphine Pain Medication Usage - Total Daily Dose (mg)								
N	47	41	42	35	39	41	36	32
Mean	739.2	433.1	544.2	584.0	602.9	534.0	557.7	608.3
SD	763.8	515.6	579.6	583.3	777.7	599.4	617.7	734.2
Median	440.0	200.0	440.0	440.0	440.0	340.8	366.7	333.3
Minimum	2.5	7.5	15.0	7.5	7.5	15.0	7.5	7.5
Maximum	3000.0	2133.3	3000.0	2400.0	4000.0	2900.0	3007.5	2925.0
Difference between means (CRFA-HA) and 95% CI	306.1 (32.6, 579.6)		-39.8 (-304.8, 225.2)		68.9 (-239.3, 377.0)		-50.6 (-378.0, 276.8)	
P-value (difference between groups)	0.0235**		0.8900**		0.8322**		0.9656**	
Change from Baseline in Non-Morphine Pain Medication Usage - Total Daily Dose (mg)								
N	--	--	32	23	28	26	27	19
Mean	--	--	-339.3	56.6	-86.0	-17.4	-89.1	71.8
SD	--	--	839.5	413.0	1104.3	537.0	706.9	595.6
Median	--	--	0.0	5.0	0.0	0.0	0.0	0.0
Minimum	--	--	-2200.0	-1133.3	-2000.0	-1233.3	-2000.0	-1166.7
Maximum	--	--	2392.5	733.3	3566.7	1300.0	2400.0	1500.0
Difference between means (CRFA-HA) and 95% CI	--	--	-395.9 (-740.9, -50.9)		-68.6 (-541.1, 403.9)		-160.9 (-561.4, 239.5)	
P-value (difference between groups)	--	--	0.0011**		0.1931**		0.4297**	
P-value (change from Baseline)	--	--	0.0105$^{\$\$}$	0.1743$^{\$\$}$	0.3463$^{\$\$}$	0.6580$^{\$\$}$	0.3038$^{\$\$}$	0.7302$^{\$\$}$

***Wilcoxon rank sum test for two independent samples, $^{\$\$}$Wilcoxon signed rank test for paired samples*