Effect of the Temperature used in Thermal Radiofrequency Ablation on Outcomes of Lumbar Facets Medial Branches Denervation Procedures: A Randomized Double-Blinded Trial

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Protocol Version 3
Revision Date: 10/15/2019

Amendments to Protocol to-date:

- Amendment 1 Dated 24MAR2014:
  "The protocol is being updated so that at the 12 month follow-up subjects who do not want to come to clinic can complete the questionnaire by mail or phone," has been added to the protocol**.**

- Amendment 2 Dated 14MAY2014:
  "Change the last item in the exclusion criteria from: k. History of previous RFA at the same level(s) in the previous 12 months. To k. History of previous RFA at the same level(s) in the previous 6 months," has been changed on the current version of the protocol.

- Amendment 3 Dated 12NOV2014:
  "The investigator would like to add a window of +/- 1 week to the 1, 3, 6 and 12 month follow ups," has been **disregarded** therefore has **not** been added to the current protocol version.

- Amendment 4 Dated 23JAN2018:
  Change inclusion criteria f. to "f. Adequate response to the diagnostic block(s), 1 or more, at the same levels of the intended block (defined as ≥70% pain relief)." – which has been updated on current protocol version.

- Amendment 5 Dated 23JAN2018:
  Adjustment to the above stated amendment dated 24MAR2014 "The protocol is being updated so that subjects who do not want to come to clinic can complete the questionnaire by mail or phone for any of the follow-up visits". This has been added to the protocol.

- Amendment 6 Dated 23JAN2018:
  Spelling mistakes and references have been corrected.

- Amendment 7 Dated 23JAN2018:
  Page numbers have been added.

- Amendment 8 Dated 23JAN2018:
  Protocol version and revision date have been added.

- Amendment 9 Dated 15OCT2019
  Protocol Version and revision date have been updated.

- Amendment 10 Dated 15OCT2019
  Change exclusion criteria I to “i. Psychopathology including uncontrolled depression, somatization or poor coping skills.”– Which has been updated on current protocol version.

Study Aims:

1. To compare the effects of 2 competing temperatures used for thermal Radiofrequency Ablation (RFA) of the lumbar facet medial branches in patients with chronic low back pain secondary to lumbar facets arthropathy.

2. This prospective study will assess the relative effects of two temperatures (in degrees Celsius) used to ablate the targeted nerves in regards to pain management and possible complications.

Research Question:

Which temperature used to produce RF lesion (80ºC or 90ºC) is associated with better overall improvement in facet-mediated chronic low back pain?

Specific Hypotheses:

- **Primary**

Lumbar facets medial branches RFA at 90ºC provides more overall pain relief (i.e. percent of improvement), when compared to ablation at 80ºC with no additional adverse events.

- **Secondary**

Ablation of the lumbar facets nerve supply at 90ºC will provide better improvement in the functionality level, general mood and quality of life as measured by VAS (Visual Analog Scale) pain score, Pain Disability Index (PDI), McGill Pain and Beck Inventory (BI) questionnaire scores than those receiving the ablation at 80ºC. Furthermore, it is associated with less opioid consumption, no additional unwanted adverse events and/or complications along with less need to repeat RFA procedure over one year follow-up period.

Significance/Importance:

Chronic lower back pain (LBP) is a significant health care issue in the United States and the world. Chronic LBP contributes to decreased quality of life, decreased functionality and increased utilization of health care resources. The causes of chronic LBP tend to be multi-factorial. Arthropathy of the lumbar facet joints is thought to be a common etiology (15-45%) (1). Radiofrequency Ablation (RFA) of the medial branch nerve of the facet joint is a well-established treatment modality used to decrease facet joint pains. However, a wide range

of temperature is being used (70-90 degrees Celsius). In addition, the optimal temperature that provides the best patient outcomes with the least side effects is not well established in the pain management literature.

Summary of Literature:

Gallagher J, Vadi PLPD, Wedley JR, et al. in 1994 studied the efficacy of the radiofrequency facet joint denervation in the treatment of LBP in a prospective controlled double-blinded study which has shown that radiofrequency is better than sham denervation in patients with clear-cut relief at 6 months and no significant difference between groups among equivocal responders (2) .While Van Kleef et al. in a prospective double-blinded study of thirty one patients had concluded that radiofrequency lumbar zygapophysial Joint denervation at 80ºC results in a significant alleviation of pain and functional disability in a select group of patients with chronic LBP, both on a short-term and long-term basis(3). On the other hand, Leclaire et al. had randomly assigned 70 patients with LBP for >3months duration to receive percutaneous radiofrequency articular facet denervation at 80ºC under fluoroscopic guidance or the same procedure without effective denervation (sham therapy). At 4 weeks, the Roland-Morris score had improved by a mean of 8.4% in the neurotomy group and 2.2% in the placebo group, showing a treatment effect of 6.2% (P=0.05). At 4 weeks, no significant treatment effect was reflected in the Oswestry score (0.6% change) or the visual analog pain score (4.2% change). At 12 weeks, neither functional disability, as assessed by the Roland-Morris scale (2.6% change) nor Oswestry scale (1.9% change), nor the pain relief, as assessed by the visual analog scale (27.6% change) showed any treatment effect (4). It should be noted that in this study, the diagnosis of lumbar facets arthropathy was made by a primary care physician rather than a pain management specialist.

In 2005, Von Wijik et al. in RCT, had found that there is no difference at 3 months between radiofrequency using temperature of 80ºC and sham denervation in combined outcome measures, however, radiofrequency patients have better Global perceived effect and back pain relief (5) . In another prospective study after positive diagnostic block, Nath et al. have found that active treatment group using 85ºC temperature has shown statistically significant improvement not only in back and leg pain but also back and hip movement as well as the sacroiliac joint test. Pre-operative sensory deficit and weak or absent ankle reflex normalized (P<0.01) and (P<0.05), respectively. There was significant improvement in quality of life variables, global perception of improvement, and generalized pain (6).

In a retrospective study done at our department, 100 patients (50.3%) received RFA at 80ºC and 99 patients (49.8%) received RFA at 90ºC. there were no clear cut advantage of either

temperature. However, the preliminary analysis did not control for potentially confounding baseline demographics and disease related characteristics. Thirty eight (38%), 9 (9%), 37 (37%) and 16 (16%) patients undergoing RFA at 80ºC reported no improvement, minimal improvement (<25%), moderate improvement (25-75%), and marked improvement (>75%) in symptoms respectively. Among patients undergoing RFA at 90ºC, these numbers were 19 (19%), 1 (1%), 44 (45%) and 34 (35%), respectively. The proportional odds logistic regression model for relief did not indicate a significant difference in relief scores between the two groups (likelihood ratio test p=0.033, using an adjusted significant difference criterion at 0.025). Due to the factors discussed and the inherent limitations of the retrospective studies, we plan to prospectively study the issue in a double-blinded randomized fashion.

Study Population:

• **Patient Population:**

Subjects with chronic low back pain (LBP) of lumbar facet joints origin fulfill the other below inclusion criteria and do not meet any of the exclusion criteria will be recruited from Cleveland Clinic Pain management outpatient clinic.

• Inclusion Criteria:

a. Age >18 years-old.

b. Subjects who are able to give informed consent and to understand and comply with study requirements.

c. Predominantly axial low back pain ≥3 months in duration with no radicular pain below the knee that failed to conservative therapy.

d. Subjects who have chronic back pain attributed to lumbar facet joints arthropathy based on clinical evaluation (paraspinal tenderness and/or facet loading test in the absence of signs and symptoms suggestive of focal neurological deficits).

e. No history of previous back surgery at the intended treatment levels.

f. Adequate response to the diagnostic block(s), 1 or more, at the same levels of the intended block (defined as ≥70% pain relief).

g. Patients who will undergo RFA of 3-4 lumbar facet medial branches on one side only.

• **Exclusion Criteria:**

a. Subjects who decline to provide written consent or follow-up.

b. Subjects who have a history of adverse reactions to local anesthetic.

c. Subjects who are pregnant.

d. Subjects with bleeding disorders or active anticoagulation that cannot be stopped for few days close to the time of the procedure.

e. Subjects who have an active systemic or local infection.

f. Presence of radicular pain extending below the knee.

g. Patients who have other specific etiology of low back pain (e.g. significant spinal canal stenosis or grade 2 or 3 spondylolisthesis).

h. Secondary gain (i.e., ongoing litigation, worker's compensation or other financial incentives).

i. Psychopathology including uncontrolled depression, somatization or poor coping skills.

j. Physical factors including non-sedentary lifestyle, e.g.; morbid obesity (BMI >35kg/m^2).

k. History of previous RFA at the same level(s) in the previous 6 months.

Subject Withdrawal:

Subjects may voluntarily withdraw from the study at any time. Reasons for withdrawal will be recorded on the appropriate case report form (CRF). Pertinent data from such patients (either before or after the withdrawal) will be included in analysis if available, unless the patient explicitly states that they do not want their data to be included.

Terminating Subject Participation:

A subject's participation in the study may be terminated if continued participation in the study is not in the subject's best interest, in the investigator's opinion.

Methods:

• **Study design:**

This will be a prospective, randomized double-blinded study.

• **Randomization:**

After Institutional Review Board (IRB) approval and written consent, eligible patients, consenting to participate in the study will be randomly assigned to one of the two study groups (80ºC or 90ºC) based on computer-generated allocations which will be done immediately before use.

• **Blinding:**

Patient, physician performing the procedure and physician or research fellow assessing the outcomes will be blinded to the group assignment.

• **Study Protocol:**

Patients must meet all inclusion and exclusion criteria to be eligible for the study. After eligibility is confirmed, the patients will receive complete information about the study both verbally and in writing. Informed consent must be obtained from the patients prior to randomization and study-specific procedures. Once all eligibility criteria are fulfilled (including informed consent), the patients will be randomized, and treatment allocation will be performed. Key baseline patients characteristics, as well as patient's eligibility criteria, will be collected on case report forms.

Randomization will be done through an independent study coordinator or research fellow other than the one who is assessing the outcomes. Patients will be randomly assigned to one of the two groups as 1:1 ratio.

The nurse who is responsible for operating the radiofrequency generator will be the only one informed about the randomization results through the unblinded study coordinator. The physician and the patient will both be blinded.

Intravenous access will be inserted for all patients and mild sedation with midazolam will be given according to the patient needs.

With the C-arm guidance a 20-gauge radiofrequency needles with 10mm active tips will be used to ablate 3-4 lumbar facet medial branches.

At each level, needles will be adjusted to optimize sensory and motor stimulation. For each nerve lesion, correct placement is confirmed using electrostimulation at 50Hz, with concordant sensation achieved at 0.5V or less. Before denervation, multifidus stimulation and the absence of leg muscles contractions is verified with electrostimulation at 2Hz.

The radiofrequency lesions will then be carried out at 80°C (group 1) or

90°C (group 2) for 90 seconds twice to produce the desired lesions of the medial branches.

• **Data Collection:**

Study data for follow-up visits will be collected by one of 3 ways. The follow-up visit questionnaires can be filled in-person, sent out to patients by mail or completed over the phone, whichever is more convenient for the patient.

Collected data will then be inputted and managed using REDCap (Research Electronic Data Capture) tools hosted at Cleveland Clinic. REDCap is a secure, web-based application designed to support data capture for research studies, providing:

1) An intuitive interface for validated data entry.

2) Audit trails for tracking data manipulation and export procedures.

3) Automated export procedures for seamless data downloads to common statistical packages.

4) Procedures for importing data from external sources.

• **Patient Demographics:**

- Age
- Sex
- Smoking
- BMI
- History of back surgeries.

- Diabetes mellitus.
- Response to diagnostic blocks

• **Patient Baseline data:**

- Preoperative and baseline pain score will be collected using Visual Analog Scale (VAS)
- Pain Questionnaires:
    - Pain Disability Index (PDI).
    - McGill Pain Questionnaire.
    - Beck Inventory (BI)
- Oral pain medications in morphine sulfate equivalent mg/day.

• **Technique related data:**

- The temperature of the probe used (80ºC or 90ºC)
- Duration of application of the RF probe is 90 seconds twice using 10mm active tip probe.
- Sensory stimulation 0.5mAmp
- Needle size 20G
- The number of ablated nerves.
- Side/Laterality.

• **Outcomes Data:**

Outcomes will be measured at baseline and 1, 3, 6 and 12 months follow-up visits post-procedure.

- **Primary outcomes:**
  Overall pain relief (i.e. percent of improvement) at each visit mentioned above.

- **Secondary outcomes:**
    - Postoperative Pain Scores in the subsequent visits using VAS at each visit mentioned above.
    - Pain Questionnaires:
        - Pain Disability Index (PDI).
        - McGill Pain Questionnaire.
        - Beck Inventory (BI)
    - Number of repeats of procedure in the first year after index procedure.

- Consumption of oral opioids in mg oral morphine equivalents recorded at the baseline before the procedure and then in the follow-ups post-procedure (1, 3, 6 and 12months).

- This table summarizes the morphine equivalent doses for the most commonly used morphine derivatives (7).

Drug Name	Oral dose equivalent to 30mg oral morphine sulfate	IV dose equivalent to 30mg oral morphine sulfate
Morphine sulfate	30 mg (1:1 ratio)	10 mg (1:3)
Hydromorphone	7.5 mg (1:4 ratio)	1.5 mg (1:20)
Meperidine	300 mg(10:1 ratio)	100 mg (3.33:1)
Methadone	12mg(1:2.5 ratio)	10 mg (1:3)
Oxycodone	15 mg(1:2 ratio)	N/A
Hydrocodone	30 mg(1:1 ratio)	N/A
Codeine	200 mg(6.66:1 ratio)	120 mg (4:1)

- The following formula will be used for Fentanyl transdermal patch:

- 25 µg/h is equivalent to 87.5 mg morphine/24h
- 50 µg/h is equivalent to 175 mg morphine/24h
- 75 µg/h is equivalent to 262.5 mg morphine/24h
- 100 µg/h is equivalent to 350 mg morphine/24h

• **Adverse Events:**

- Persistent paresthesia (yes/no)
- Nerve injury (yes/no)
- Infection (yes/no)
- Bleeding (yes/no)

• **Data Analysis:**

Standard descriptive statistics will be used to compare the randomized groups on baseline variables. Any obviously imbalanced co-variables (say, with a standardized difference greater than 0.20 in absolute value) will be adjusted for in both primary and secondary analyses. Our primary analysis will be intent-to-treat.

- **Primary Hypothesis:**

Graphically displayed over follow-up times (1, 3, 6 and 12 months) using boxplots containing the median, quartiles and outliers. At each follow-up time point (1,3, 6 and 12 months) we will assess whether 80°C and 90°C RFA temperatures differ with respect to the percentage of pain relief using the Wilcoxon rank-sum test. The significance criterion will be 0.05/4=0.0125 at each time, using a Bonferroni correction to control the type I error at 0.05 for the primary hypothesis. In addition to the P-value, the estimated median percentage of pain relief for each group and difference in medians with confidence intervals will be reported. The estimated probability of pain relief at 90°C being better than at 80°C with confidence interval will be reported, since the Wilcoxon rank sum test has a null hypothesis that this probability is 0.50. All the confidence intervals will be estimated based on bootstrapped standard error with 10,000 bootstrap replications (8).

- **Interim analyses:**

Interim analyses will be conducted for efficacy and futility at each 25% of the maximum enrollment (see Sample Size Considerations) using a group sequential design and gamma spending function (using gamma = -4 for efficacy and -2 for futility). P-value boundaries for efficacy (futility in parentheses) will be $P \leq 0.0016$ ($P > 0.957$), $P \leq 0.0048$ ($P > 0.719$), $P \leq 0.0147$ ($P > 0.239$), and $P \leq 0.0440$ ($P > 0.0040$) at looks 1 through 4, respectively.

- **Secondary hypotheses:** We will compare randomized groups on the following variables:

VAS pain scores/Pain Disability Index (PDI)/McGill Pain questionnaire scores/Beck Inventory (BI) scores.

While the detailed description below focuses on the VAS pain score outcome for brevity, the analysis approach will be the same for Pain Disability Index (PDI), McGill Pain questionnaire scores, and Beck Inventory (BI) scores.

Graphical analysis will be undertaken to describe the degree of pain reduction observed in patients undergoing each treatment. The association between RFA temperature and pain reduction will be performed using a mixed effects model adjusting for time interval and also for baseline pain score to increase precision. We will assess the group-time interaction and assess treatment effects at each time if interaction $P < 0.15$. The mixed model will account for potential intra-subject correlation of repeated VAS pain measurements within a patient using a spatial

correlation structure. A model-based Wald test for regression model coefficients will be used to evaluate whether or not RFA temperature affects mean pain reduction.

- **Opioid Consumption:**

As preliminary retrospective study showed, postoperative opioid consumption is largely binary in nature for this patient's population, as over 60% of our patients did not take any opioids. Thus, postoperative opioid consumption within a year of the first RFA will be analyzed as a binary outcome, i.e., any versus none (however, dosage information among the subset of patients taking any opioids will be described using medians and quartiles for each group). Multivariable logistic regression will be used to estimate the adjusted relative risk for postoperative opioid use comparing patients undergoing RFA at 90°C to patients undergoing RFA at 80°C. A logistic model-based Wald test for regression coefficients will be used to test the hypothesis of the effect of temperature on the postoperative opioids use (i.e., whether or not the relative risk is different from a value of 1.0).

- **Number of repeat of RFA procedures**

Need for repeated RFA procedure over one year period will be analyzed as a count variable using a proportional odds logistic regression model. If the number of repeats greater than 1 is very rare, we will use a binary outcome of any RFA procedure comparing two groups of patients.

- **Complications:**

Incidence of each individual complication will be reported for each group, with confidence intervals. Possible adverse events (persistent paresthesia, nerve injury, bleeding and infection) will be summarized into a single composite binary outcome, i.e., any versus none. The risk of experiencing one or more adverse events will be compared between RFA at 90°C and RFA at 80°C groups using logistic regression.

Type I error will be controlled at 5% for the secondary outcomes using the Bonferroni correction for simultaneous hypotheses. SAS 9.3 software (SAS Institute, Cary, NC) and R statistical software version 2.7.2 (The R Foundation for Statistical Computing, Vienna, Austria) will be used for all analyses and graphics.

- **Sample size considerations:**

Sample size estimation is based on the frequency distribution estimated across four categories of pain relief used in our preliminary retrospective study. Thus, for these calculations 38%, 9%, 37%, and 16% of patients undergoing RFA at 80°C are assumed to develop no improvement (=0%), minimal improvement (<25%), moderate improvement (25-75%), and marked improvement (>75%) in symptoms, respectively. We further assumed that the data was uniformly distributed across each category through simulation, and performed power calculations on the simulated data using categories of percent pain relief of 0, 1-10, 11-20, 21-30, …, 91 – 100. In order to have 90% power at the 0.0125 significance level at each time point (0.05/4 = 0.0125 at each time point) to detect a clinically significant shift in improvement of absolute 15% between RFA at 90°C and RFA at 80°C, a maximum of N=216 total patients would be required. Below we list the proportion of patients in each percent pain relief category as assumed for the sample size calculations described above. Although a 20% increase is in general what would be considered a clinically important improvement in pain relief, we plan for 15% since there may be a nontrivial fraction of patients who experience no relief in either group. Adjusting for 3 interim analyses and a final analysis would require a maximum of N=237. With the above parameters, there will be a cumulative 8%, 37%, 75%, and 100% chance of crossing a boundary at the 1st through 4th analyses if the alternative hypothesis is true as stated above.

Group	0	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100
Control	.38	.041	.035	.06	.07	.067	.069	.087	.062	.057	.072
Experimental	0	0	.399	.041	.03	.083	.068	.064	.077	.078	.16

We plan to re-estimate sample size after obtaining at least 1 and 3 month continuous pain relief outcome for the first 60 patients, using the observed shape of the distribution and the variability of the outcome, but still based on an absolute 15 percent upward shift from the 80 degrees group. Type I error will be controlled using the methods in Kieser 2000 (9).

We will provide results to the Data and Safety Committee on efficacy and safety assessments, including conditional power analyses, but the committee will have final say on whether the study would progress to the next interim analysis or be stopped.

References

1. Schwarzer AC, Aprill CN, Deby R et al. Clinical features of patients with pain stemming from the lumbar zygapophysial joints. Is the lumbar facet syndrome a clinical entity? Spine 1994; 19: 1132-1137.

2. Gallagher J, Vadi PLPD, Wedley JR, et al. Radiofrequency facet joint denervation in the treatment of low back pain: a prospective controlled double blind study to assess its efficacy. Pain Clinic 1994; 193-8.

3. Van Kleef M, Barndse GA, Kessels A, Voets HM, Weber WE, De Lange S. Randomized trial of radiofrequency lumbar facet denervation for chronic low back pain. Spine 1999; 24: 1937-42

4. Leclaire R, Fortin L, Lambert R, Bergeron YM, Rossignol M. Radiofrequency facet joint denervation in the treatment of low back pain: a placebo- controlled clinical trial to assess efficacy. Spine 2001; 26: 1411-6; discussion 17.

5. Van Wijk RM, Geuts JW, Wynne HJ, et al. Radiofrequency denervation of lumbar facets joints in the treatment of chronic low back pain: randomized, double –blind, sham lesion-controlled trial. Clin J Pain 2005; 21:335-44.

6. Nath s, Nath CA, Pettersson K. Percutaneous lumbar zygapophysial (facet) joint neurotomy using radiofrequency current, in the management of chronic low back pain: A randomized double blind trial. Spine (Phila PA 1976); 33 (12): 1291-1297; discussion 1298, 2008.

7. Vieweg WV, Lipps WF, Fernandez A. Opioids and methadone equivalents for clinicians. Prim Care Companion J Clin Psychiatry 2005; 7: 86-88.

8. Efron B and Tibshirani R. An introduction to the bootstrap. Monographs on statistics and applied probability. 1993, New York: Chapman & Hall. xvi, 436 p.

9. Kieser M, Friede T: Re-calculating the sample size in internal pilot study designs with control of the type I error rate. Statistics in Medicine 2000; 19: 901-911