Intercostal Nerve Cryoablation for Postoperative Pain Management

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I. PROTOCOL TITLE

Intercostal Nerve Cryoablation for Postoperative Pain Management

II. PRINCIPAL INVESTIGATOR & RESEARCH TEAM

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III. STUDY SITE

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   McGovern Medical School at UTHealth
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IV CONTACT INFORMATION

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V. RESEARCH SYNOPSIS

A. Clinical Phase

Phase IV

B. Study Population

The study will include patients aged 18 and over, all gender and race, who require thoracoabdominal incisions undergoing the descending thoracic or thoracoabdominal aortic aneurysm repair.

C. Study Design

Prospective single-blinded, controlled randomized clinical trial with 2-armed parallel-group sequential design

D. Sample Size

20

E. Study Duration

13 months

F. Study drug and Intervention Description

We will use CryoICE® CRYO2 cryoablation probes (AtriCure, Inc), which is an FDA-approved device for the use of intercostal nerve cryoablation.

Subjects will be randomized into two groups:

Group A will receive the study procedure, intercostal nerve cryoablation using CryoICE® CRYO2 cryoablation probes (AtriCure, Inc) to intercostal spaces 4th to 10th in thoracoabdominal aortic repairs and 4th to 8th in descending thoracic aortic repair cases. This procedure will be performed under electromyography to confirm the successful ablation of the nerve.

Group B will not receive cryoablation but will obtain electromyography to evaluate as the control.

Both patient groups will receive intraoperative local analgesia infiltration with bupivacaine liposomal injectable suspension (Exparel®, Pacira Pharmacoceuticals) and patient-controlled analgesia (PCA) postoperatively.

H Primary Objectives

The primary objective of the study is to prove the feasibility of intercostal nerve cryoablation in postoperative pain control both in magnitude and duration in patients undergoing thoracoabdominal incisions for the descending or thoracoabdominal aortic aneurysm repair.

I. Secondary Objectives

- To compare opioid use between groups.
- To evaluate and compare patient participation in physical therapy.
- To evaluate and compare patient length of stay in hospital.
- To evaluate cost-effectiveness of adding intercostal nerve cryoablation to a postoperative pain control regimen.

VI. BACKGROUND AND SIGNIFICANCE

General Information

This is a pilot study to prove the efficacy of intercostal nerve cryoablation during the descending/thoracoabdominal aortic repair with thoracoabdominal incisions to have better control of postoperative pain management.

Background Information

In the United States, around 48 million inpatient surgical procedures were performed in 2009.[1] Although pain is a predictable part of the postoperative experience (significant in up to 75% of patients),[2,3] inadequate management is still common. Adequate postoperative pain management has shown to improve healing period, contribute to faster patient mobilization, and reduce the hospital length of stay and healthcare cost.[4-6] Some studies show that the economic load of chronic pain that develops from an acute episode of pain in a 30 year-old patient may be as much as $1 million over a lifetime.[7] Lack of postoperative pain control may also result in deep vein

thrombosis, pulmonary embolism, coronary ischemia, myocardial infarction, pneumonia, poor wound healing, insomnia and demoralization.[8,9] A number of drugs are available for postoperative pain control, such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDS), local anesthetic agents infiltration, as well as combined regimens and protocols among them. Opioid use is the backbone of postoperative pain control but it does not come without risks. Severe opioid side-effects such as respiratory and central nervous system depression must be accounted for when overdose can cause renal impairment. Acetaminophen (Tylenol®) is generally safe but high doses can cause hepatic toxicity. One of the limitations of many pain control regimens, including most local anesthetic infiltrations, is that the effect usually lasts for less than 8 hours only.[10,11] In our recent trial using liposomal formulation of bupivacaine for extended release, with a hope to have improved post-thoracotomy pain, which also failed to show adequate pain control. The liposomal formulation may have extend the effect of local anesthesia up to 48 hours, but was not sufficient to have satisfactory outcomes. The Patient Controlled Analgesia (PCA) method is one that is very commonly used in postoperative pain management protocols. This method was developed and introduced by Philip H. Sechzer in the late 1960s and described in 1971. It consists of allowing people to administer their own pain relief whenever they feel it is needed. On the surgical patient and while in hospital, the usual administration route is IV (intravenous), and the drugs usually used on a PCA system are from the opioid family. The infusion is programmed by the prescriber in terms of demand dose, lockout interval, maximum drug delivery per hour, and rescue dose. For example, a morphine PCA could be set to deliver 1 mg of morphine sulfate on demand after a lockout interval of 10 minutes, a maximum cumulative dose of 8 mg per hour, and a rescue dose of an extra 2 mg to be given if there is inadequate pain control. If it is set and functioning as intended, the machine is unlikely to deliver an overdose of medication.

Cryoanalgesia has been used to treat pan syndromes including facial neuralgias and peripheral neuropathies.[12] In the 1980s, this technique was applied for postoperative pain control in patients with thoracotomy with satisfactory improved pain control without adverse events.[13,14] The Food and Drug Administration (FDA) approved

the first commercially available cryoablation probe (CryoICE®, AtriCure, Mason, OH), which made the cryotherapy more applicable. Postoperative pain management of thoracoabdominal incisions is the most invasive incision and pose a difficult challenge to manage pain control. Thus, we propose a pilot study to investigate the effectiveness of intercostal nerve cryoablation for postoperative pain control. This pilot study will lead to an estimate on its efficacy and utilization as an option for the postoperative pain management using the cryoablation. We will perform a larger prospective randomized study if this pilot study demonstrates the efficacy of the procedure.

VII. PRIMARY OBJECTIVES

The primary objective of the study is to prove the feasibility of intercostal nerve cryoablation in postoperative pain control both in magnitude and duration in patients undergoing thoracoabdominal incisions for the descending or thoracoabdominal aortic aneurysm repair.

Specific assessment tools that will be used in our study are:

1. Numeric Pain Scale (NPS): The NPS measures the intensity of pain. It consists of an 11-point scale from 0-10, where 0 means no pain and 10 means the most intense pain imaginable. Patients verbally select a value that correlates to the pain experienced by them. A written form can also be used. The NPS has good sensitivity and has a good capacity of producing data that can be statistically analyzed.[15,16,17,18]

2.Brief Pain Inventory (BPI): The Brief Pain Inventory is a medical questionnaire used to measure pain, developed by the Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care. Although the BPI is derived from the NPS it is more comprehensive and expanded. Besides assessing pain intensity, it assesses how much the pain is affecting their lives. The BPI is a powerful tool and, having demonstrated both reliability and validity across cultures and languages, is being adopted in many countries for clinical pain assessment, epidemiological studies, and in studies of the effectiveness of pain treatment.[19,20]

3. Five-point satisfaction scale: This scale is used to assess the patient's pain management experience during their postoperative care. It consists of patients rating

their overall postoperative pain management experience using a 5-point rating system. The scale is from 1 to 5 with 1 being “extremely dissatisfied”, 2 “somewhat dissatisfied”, 3 “Neutral/Neither satisfied nor dissatisfied”, 4 “somewhat satisfied” and 5 “extremely satisfied” with their postoperative pain care. This rating has been used in other clinical trials of different analgesia to be a reproducible assessment tool.[21]

Primary outcome measures

- The area under the curve (AUC) of Numeric Pain Scale (NPS) scores through 72 hours after intraoperative injection– Each subject, using the numeric scale from 0 to 10 (11 numbers, 0 being no pain, and 10 the highest pain) will self-assess pain level at (+/-2 hours) 7am and 7pm of the third to fifth post-operative days. The AUC on a graphical plotting will be used to analyze data.
- Brief Pain Inventory (BPI) – Each subject will be asked to complete the BPI before the procedure, at 7am (+/-2 hours) of the third to fifth post-operative days as well as on their 30th and 180th post-operative days.
- 5-point satisfaction scale – Each subject, using a 5 number (1 to 5) scale will be assessed on post-surgical analgesia satisfaction (from 1 being “very dissatisfied” to 5 being “very satisfied”). Patients will be assessed using this method around 7am of the third to fifth post-operative days and as well as on their 30th and 180th post-operative days.

VIII. SECONDARY OBJECTIVES

- To compare opioid use between groups.
- To evaluate and compare patient participation in physical therapy.
- To evaluate and compare patient length of stay in hospital.
- To evaluate cost-effectiveness of adding intercostal nerve cryoablation to a postoperative pain control regimen.

Secondary outcome measures

- The total amount in mg of opioid medication consumed through third to fifth post-operative days after surgery.
- Requirement of opioids at the time of discharge

- Requirement of PCA use and amount of PCA used
- Patient participation during physical therapy rehabilitation duration to reach an optimal functional level
- Length of hospital stay
- Hospital cost for patient care during hospitalization will be estimated from hospital charges and financial records.

IX. STUDY POPULATION

The target population of our study will be comprised of patients that are 18 years-old and above that present to our group at the McGovern Medical School at UTHealth and will require thoracoabdominal incision for the descending/thoracoabdominal aortic aneurysm repair. Our plan is to enroll 20 patients over a period of 6 months.

Inclusion/Exclusion Criteria

Patients will be eligible for the study if:

- 18 years-old or older, and
- Descending/thoracoabdominal incision is planned
- There is reasonable expectation that the patient will be extubated within 48 hours after surgery

Patients will be excluded from the study if:

- The patient has a known allergy to morphine or any opioid
- The patient has a known chronic pain disorder or takes daily opioid medication > 1 month prior to surgery
- The surgeon/anesthesiologist concludes that the period for intubation will be likely be for more than 48 hours after surgery There is anticipated difficulty communicating pain status due to language or other barriers at the investigator discretion.

Protocol Deviation:

It will be considered a protocol deviation if patients receive, during the first three days after surgery, any type of analgesic other than opioids.

Withdrawal criteria:

- Voluntary: patients who had consented and enrolled in the trial will maintain their right to withdraw at any point during the study as explained in the informed consent.
- In case of unexpected/unpredicted

X. STUDY DRUGS

CryoICE® CRYO2 cryoablation probe (AtriCure, Inc) is an FDA-approved device for the use of intercostal nerve cryoablation. Subjects will be randomized into two groups: Group A will receive the study procedure, intercostal nerve cryoablation using CryoICE® CRYO2 cryoablation probes (AtriCure, Inc) to intercostal spaces 4th to 10th in thoracoabdominal aortic repairs and 4th to 8th in descending thoracic aortic repair cases. This procedure will be performed under electromyography to confirm the successful ablation of the nerve.Group B will not receive cryoablation but will obtain electromyography to evaluate as the control.

Both patient groups will receive intraoperative local analgesia infiltration with bupivacaine liposomal injectable suspension (Exparel®, Pacira Pharmacoceuticals) and patient-controlled analgesia (PCA) postoperatively.

XI. STUDY SCHEDULE

Expected start date: Jan 1st, 2019

Expected end-date for enrollment: June 30th, 2019

Length of enrollment for each patient: 6 months

Length of follow-up for each patient: 6 months

Expected end-date of study: January 31st, 2020

XII. STUDY DESIGN/METHODOLOGY

This will be a single institution, prospective, single-blinded, randomized, controlled effectiveness study with 2-armed parallel-group sequential design to assess the efficacy of intraoperative intercostal nerve croyablation in postoperative pain control when compared to our current standard care, local anesthesia infiltration of Exparel®.

Screened patients meeting the eligibility criteria will be randomized into one of the two study groups. Both patient groups will receive intraoperative local analgesia infiltration with Exparel® prior to wound closure and patient-controlled analgesia (PCA) postoperatively. Each patient will choose whether or not they will use PCA. The first group (A) of patients will receive intraoperative intercostal nerve cryoablation using CryoICE® CRYO2 cryoablation probes (AtriCure, Inc) to intercostal spaces 4th to 10th in thoracoabdominal aortic repairs and 4th to 8th in descending thoracic aortic repair cases prior to wound closure. This procedure will be performed under electromyography to confirm the successful ablation of the nerve. The second group (B) of patients will be injected with Exparel® in the surgical wound. We will obtain intraoperative electromyography to evaluate as the control.

On the screening visit, patients should present prior to surgery to receive training on the NPS and BPI and to be assessed on their preoperative baseline pain level, using BPI. This may be performed prior to surgery in the preoperative holding area, on the inpatient ward, or in the outpatient settings of the McGovern Medical School at UTHealth.

Patients from both groups will receive the same volume of diluted Exparel®, which will be given in four 20ml syringes using 22-gauge needles (266mg of liposomal bupivacaine, equivalent of one 1.3% 20ml vial of EXPAREL, diluted in 50ml of preservative-free normal (0.9%) sterile saline for a total volume of 70ml). Intercostal muscle electromyogram will be performed in both groups. Group A will have it done before and after the cryoablation. This assessment is to confirm the completeness of the intercostal nerve cryoablation, as the waveform of the electromyogram is expected to disappear after an adequate cryoablation. Group B will have the electromyogram prior to wound closure. The surgical wound length will

be measured. Patients will be injected according to the surgical incision required. Patients that require thoracotomies or thoracoabdominal incisions will undergo serial intercostal nerve blocks. Intercostal nerve block will be done injecting 10 cc (of the total 70cc) on each side of the incision, from two above to two below the incision (total 50 cc for intercostal nerve block). In addition, all patients (including all surgical incisions) will be injected in the fascia, subcutaneous tissues, periosteum (if applicable) and parietal pleura (if applicable). The total volume injected will be 70cc regardless of incision type.

All patients will be blinded to having the cryoablation or not. The surgical team will be blinded up only until the time of wound closure as the knowledge of cryoablation is inevitable.

Patients will have access to the standard PCA (Patient-Controlled Analgesia) offered at the Memorial Hermann Hospital – Texas Medical Center. The PCA drug will be Dilaudid (hydromorphone). Initial dosing will be per the standard hospital protocol of 0.2 mg demand dose, 10-minute lockout, 2 mg per hour max, 0.4 mg rescue dose. Adjustments to the PCA dosing will be made based on clinical needs. Patients will receive PCA until the third postoperative day, and at that point, PCA will be switched to an oral analgesic, at the health-care team discretion. Modifications to the PCA regimen can be made by the health care team based on clinical need and will not be deemed a protocol deviation.

Pain assessment should start just after the patient is extubated and can adequately evaluate his/her own pain through the Numeric Pain Scale. NPS will be repeated and recorded at: twice daily (AM and PM) during the third and fifth post-operative day. NPS will also be done right before the first opioid rescue medication postoperatively (if applicable and if NPS had not been assessed within the last hour).

Patients in the study should also complete the Brief Pain Inventory (BPI) before the procedure, at (+/- 2 hours) of the during the third and fifth post-operative day, as well as on their 30th and 180th post-operative days. Patients will be assessed on their satisfaction with the postsurgical analgesia. This will be done using the 5-point satisfaction scale with 1 being “very dissatisfied” to 5 being “very satisfied” at

7am (+/- 2 hours) of the third to fifth post-op day and as well as on their 30th and 180th post-operative days. After the 180-day follow-up and BPI reporting, the patient terminates his/her enrollment. This enrollment termination does not mean severance of the physician-patient relationship. Patients will be consented and their medical records pertinent to the study will be collected on a case report form and this information will be kept on a secured HIPAA-compliant web-accessed database. No protected health information (PHI) will be maintained on the web-accessible database.

Study Conduct

1. Screening

The research group will assess patients as possible candidates for enrollment based on the inclusion criteria and the planned surgical exposure: median sternotomy, thoracotomy, midline laparotomy, and/or thoracoabdominal incision. Once the eligibility is met, an informed written consent will be collected. A member of the research team - the PI, Co-PI, research coordinator, or nurse will obtain the consent from the surgical candidates who met the preliminary inclusion criteria. The consent process will take place either during the preoperative clinic visit, upon inpatient admission, or in the preoperative holding area. Patients will be consented before their surgical procedures and will be given the appropriate time to think and discuss with family about being part of the study. There will also be given enough time for the patients to ask questions about the protocol and research study. A copy of the signed informed consent shall be provided to the patient, a copy will be placed in the patient's hospital chart, and a copy will be kept by the research team. Medical/surgical history, vital signs measurements, drug/alcohol screening, and standard preoperative testing will also be performed as per the usual surgical practice.

2. Quality of life assessment - Brief Pain Inventory

The impact of pain on patient's quality of life will be assessed through a brief pain inventory (BPI) that should be done before surgery, at 7am (+- 2 hours) of the third to fifth post-operative day as well as on their 30th and 180th post-operative days. The BPI

will be presented in an easy to comprehend questionnaire for the patients to quantify and communicate their pain experience and how it is affecting their life. It is designed such that patients with 6th-grade education should be able to complete the questionnaire on their own. Question and answers will be provided in a check-box format. The BPI that will be used on this study will be the short version. Patients with difficulty reading or who are physically unable to complete the questionnaire will be assisted by the research team based on their verbal responses to the BPI questions.

4. Enrollment

After the screening is done, the eligibility criteria are met, and the patient is consented; the patient will be enrolled in the trial. At this point, the study coordinator/research office will be notified so that the patient can be randomly allocated to one of the study groups.

5. Randomization and Allocation Concealment

Randomization and allocation concealment will be performed via a web-based/computer generated block randomization sequence/list secured in a password-protected secure computer in the trial office accessible only to the research staff independent of the trial administration process, who are not involved in the recruitment, data collection, analysis, assessment and/or follow-up. This office/research staff will be contacted by the blinded research assistant/investigator to provide certain specific

6. Preoperative assessment

Pain assessment will be also done using the BPI form.

7. Follow-up

After the surgical procedure is done, the follow-up will be:

i. 7am (+ or - 2 hours) of the third post-op day: the NPS and the the BPI and 5 -point scale analgesia satisfaction survey will be assessed

ii. 7pm (+ or - 2 hours) of the third post-op day: the NPS will be assessed

iii. 7am (+ or - 2 hours) of the fourth post-op day: the NPS and the the BPI and 5 -point scale analgesia satisfaction survey will be assessed

iv. 7pm (+ or - 2 hours) of the third post-op day: the NPS will be assessed

v. 7am (+ or - 2 hours) of the fifth post-op day: the NPS and the the BPI and 5 -point scale analgesia satisfaction survey will be assessed

vi. 7pm (+ or - 2 hours) of the fifth post-op day: the NPS will be assessed

vii. 30 days after the procedure, the BPI and 5-point scale analgesia satisfaction survey will be assessed.

xiii. Final visit, 180 days after procedure, the BPI and 5-point scale analgesia satisfaction survey will be performed.

8. Termination of enrollment

Patient will be considered to have his/her enrollment terminated:

i. After the 180-day follow-up visit, or

ii. If follow-up is lost after several attempts to contact patient, or

iii. If any medical/surgical/environmental condition develops that would affect or impair primary or secondary outcomes measurements results, or

iv. If the study is terminated, or

v. If the patient dies.

9. Termination of Study

i. End of study period

ii. If a clinically/statistically significant difference is achieved early during an interim analysis.

XIII. ADVERSE EVENT REPORTING

Patients enrolled in the trial will be informed to report any unwanted effect at any time during the study. Adverse effects of intercostal nerve cryoablation will be made plain to the patients during the screening/enrollment as well as in the informed consent process. Most adverse side effects are injury of the lung or other surrounding organs/tissues, which may happen if cryoablation probe is misplaced to the organ/tissue. This is extremely rare amongst trained and board-certified vascular surgeons. All the surgeons involved in our study have been extensively trained on the cryoablation technique required for appropriate use. Other adverse effects include

allodynia like-pain after the degeneration of the affected nerve is reported after cryoablation of the nerve, but this is often associated with thoracotomy procedure and not specific to the cryoablation. Safety monitoring will include assessment of:

i. Adverse Effects (AE)

ii. Vital Signs

iii. Wound healing status

iv. Scarring

v. Cardiac monitoring

All items above will be closely monitored in a continuous manner, as part of our standard postoperative care. Any abnormalities found will be promptly assessed and described in the patient's medical records. Once the patient is discharged it is very unlikely that any of the study drugs or procedure will cause any abnormalities. Despite this fact, patients will be asked to contact the hospital in case they feel anything unusual. Definitions and examples of the standard or known adverse events associated with cryoablation is tingling, burning sensation, etc., will be presented to the patient for reference. Patients will be also assessed on the above items on their postoperative clinic visits. In addition, emergency contact information of the office in order to speak to someone regarding documentation of these adverse events will be provided. If need be, an immediate unscheduled visit shall be arranged if the patient so desires. The PI will review AE as they occur, changes to the study design or drug use will be determined on an ongoing basis.

XIV. STATISTICAL ANALYSIS PLAN

A. Primary Outcomes

NPS measures will be plotted for each subject over the initial third to fifth postoperatively and the area under the curve (AUC) integrated to produce a cumulative numeric pain score. The primary endpoint will be measured by a statistical comparison of AUC between the groups, using a Wilcoxon rank-sum test. Randomization is expected to balance the groups with respect to preoperative risk factors.

B. Secondary Outcomes

Cumulative dose of opioid medication will be assessed as the sum of morphine doses dispensed by PCA pump during the admission. In addition, we will evaluate the amount of opioid usage using morphine milligram equivalences.[22] This will be compared by unpaired t test. We will also evaluate for the opioid prescription need at the time of discharge, and will be compared by chi-square test. Length of hospital stay will be transformed to log scale to normalize the distribution if necessary and will be compared between groups by an appropriate unpaired statistic. Attainment of physical therapy goal that justifies discharge from inpatient physical therapy within 72 hours will be assessed by an appropriate contingency table test.

C. Sample Size Determination

This is a pilot study to prove the feasibility of intercostal nerve cryoablation in patients undergoing the descending/thoracoabdominal aortic aneurysm repair with thoracoabdominal incision.

Although the study is designed as a pilot trial to collect preliminary data for assessment of feasibility, the proposed sample size of 20 subjects would be large enough to detect a seven point decrease (from 21 to 14) in the cumulative three-day postoperative BPI, with 80% power at alpha <0.05. This would equate to an average reduction of roughly two points per day in the 10-point pain scale over three postoperative days, or about a 1/3 reduction in total pain during that period with cryoablation compared to the control treatment. These estimates are based on prior work by our group with a randomized trial of injectable liposomal bupivacaine (the control treatment in this trial). This would be a large effect, but certainly within the realm of feasibility.

XV. ETHICS

A. Informed Consent Process

All eligible patients who meet the inclusion criteria will be consented, if willing, after an in-depth description of the study, the study drug and its adverse effects, the risks and benefits, follow-up routine, enrollment and termination terms. The importance of follow-

up will be emphasized; however, the patient will retain the right to voluntarily withdraw from the study at any point. It will also be stressed that patient confidentiality will be kept at all times during study through de-identification of data. Information will be stated clearly in a written consent form that will be designed at a 6th grade level of understanding. Information will also be presented verbally. A member of the research team, either the principal investigator, or co-investigators will obtain the consent of the patient or other the legally authorized representative of the patient. The consent process will take place either during the preoperative clinic visit, upon inpatient admission, or in the preoperative holding area. The member of the team who is obtaining the written consent will describe the research project in its entirety and answer the questions of the patient and/or family members should they ask any. Sufficient time will be provided to the patient party to review the study before making an informed decision to participate or decline. We will make sure the patient have time to deliberate on the risk/benefits of joining the study. If they require, patients will be given at least one hour for deliberation and discussion with the research staff, friends and/or family members about enrolling or not the study Should they decide to participate, three copies of the consent form would be attested by the patient or legally authorized individual for the patient's medical record, the study record, and one copy will be provided to the patient.

B. Data Handling and Keeping

The study will be conducted in compliance with all HIPAA guidelines to protect patient confidentiality. All sensitive information or patient identifiers will be stored in form of a patient linkage file that will link the patient study/trial number to their clinical records and secured on the Zone 100 drive on specific networked computers of our department. We have a password protected electronic database that, along with the case report forms, will be de-identified and contain only study relevant data points and the patient's trial number. Access to any data pertaining to the study will be restricted to approved research team members, the FDA, institutional review boards of the McGovern Medical School at UTHealth and Memorial Hermann Hospital.

C. Risk/Benefits

Risks to participants

There is a small increased risk to the patients by participating in the study in addition to a possible chance of breach in patient confidentiality as the study involves evaluation of an FDA-approved device. As detailed in the informed consent, the subjects are at risk of developing adverse effects from cryoablation, abdominal muscle bulging or sympathetic nerve pararesis. Patients will be offered standard optimal medical therapy options, even if that will culminate in withdrawal from the study. In addition, there is risk of an unintentional disclosure of personal health information.

Benefits to participants

The patients stand to receive no direct benefit from the study. However, in the event our results endorse the published reports of reduction in postoperative pain by cryoablation, the group of patients receiving it might be indirectly benefitted through participation.

XVI. STUDY TIMELINE

Considering our group's monthly average for the given procedures and the enrollment rates, drop-outs and withdrawal, and interim analyses we estimate recruitment of our sample size will take 6 months. Once the follow-up of all enrolled participants is finished, data will be analyzed and published. The following is a chronological estimate of the stages:

Stage 1: Patient screening and enrollment 0 - 6 months

Stage 2: Follow-up up to 180 days from the last patient enrolled (0 – 12 months)

Stage 3: Data collection and analysis 1 month

Stage 4: Presentation and publication period (at the end of data analysis)

XVII. QUALITY CONTROL AND ASSURANCE

The PI will be responsible for monitoring the progress and safety of this pilot trial. Any serious or unanticipated events will be reported in a timely manner to the CPHS.

XVIII. CONFLICT OF INTEREST

There is no relationship between the principal investigator or any other research staff member and AtriCure Inc. The 10 probes are provided from the AtriCure Inc. for the current study.

XIX. FUTURE PUBLICATION AND PRESENTATION

The results of this study will be analyzed and published after the approval of the principal investigator and biostatistician in a peer-reviewed scientific journal and/or presented at an international/national scientific conference or meeting regardless of outcome. The publication will acknowledge members of the study research group for their contributions and will maintain patient data protection.

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