WOMEN'S HEALTH INSTITUTE
DEPARTMENT OF GYNECOLOGY
CLEVELAND CLINIC FLORIDA

EFFECT OF COLD THERAPY IMPLEMENTATION ON MULTI-MODAL POSTOPERATIVE PAIN MANAGEMENT IN WOMEN UNDERGOING LAPAROSCOPIC HYSTERECTOMY: A PILOT STUDY

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number or Version: _____3_____

Protocol Date: _____12/27/2016_____

EFFECT OF COLD THERAPY IMPLEMENTATION ON MULTI-MODAL POSTOPERATIVE PAIN MANAGEMENT IN WOMEN UNDERGOING LAPAROSCOPIC HYSTERECTOMY: A RANDOMIZED CONTROL TRIAL

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Investigator:

Signed:	**Pamela Frazzini Padilla, M.D., MIGS Fellow**	**Date:**	**12/27/2016**
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ABBREVIATIONS

In order of appearance

MIGS Minimally Invasive Gynecologic Surgery
ERAS Enhanced Recovery After Surgery
POD Postoperative Day
NRS Numeric Rating Scale
ASIS Abdominal Surgery Impact Scale
PACU Post-anesthesia Care Unit
EHR Electronic Health Record
SRS Surgical Recovery Scale
PSIL Pain Score and Intervention Log
IRB Institutional Review Board
CCF Cleveland Clinic Florida
CRF Case Report Form

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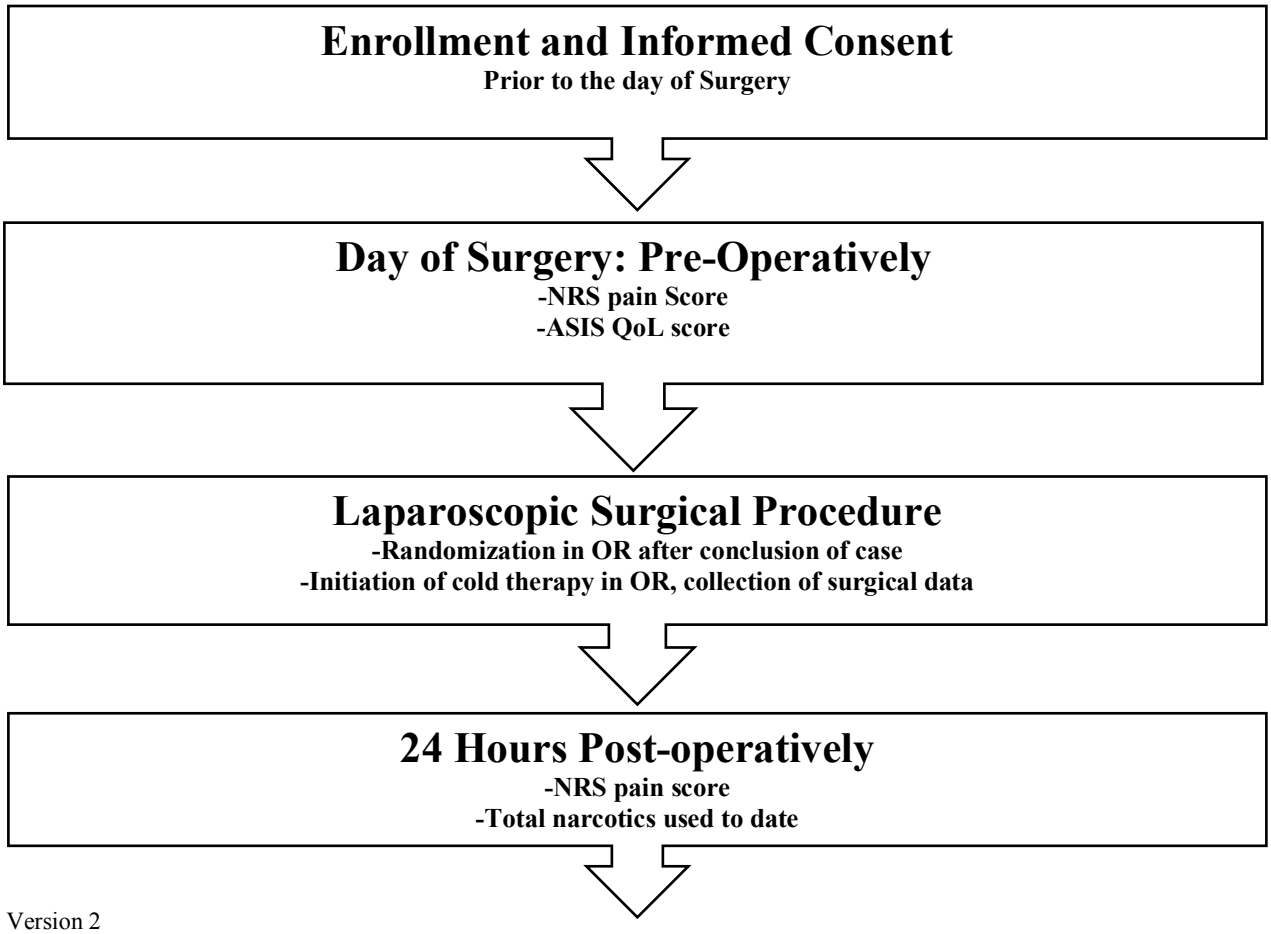
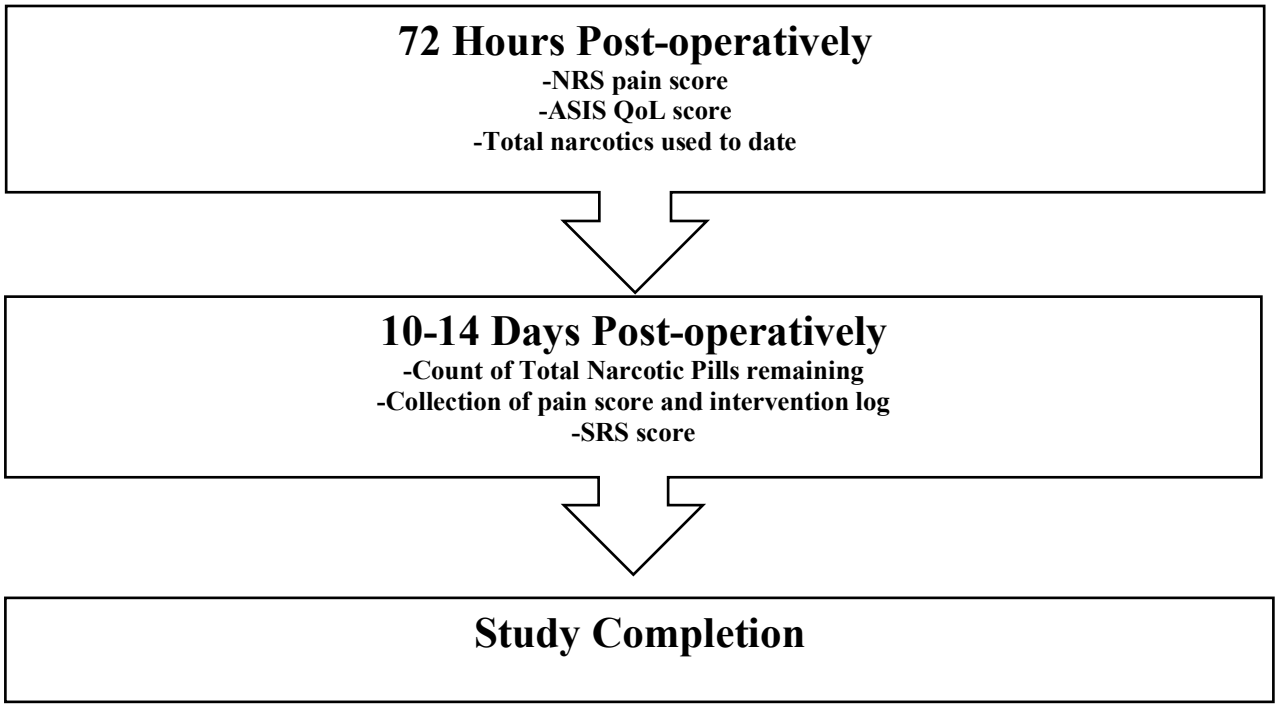
RESEARCH SCHEMA





1.0 INTRODUCTION

1.1. Background

Pain is an inevitable side effect following a surgical procedure. Post-operative pain arises from local tissue trauma and inflammation, which subsequently activate surrounding nociceptive pain receptors.[1, 2] Providing adequate analgesia to reduce post-operative pain is important for recovery by improving outcomes, increasing patient satisfaction and reducing the risk of chronic pain.[3, 4] Evidence suggests, however, that less than half of patients undergoing surgery report adequate post-operative pain relief.[5]

The goal of postoperative pain management is to relieve pain while keeping side effects to a minimum. Narcotics, although often necessary, are well known for their side effect profile including sedation, respiratory depression, nausea, vomiting, pruritus, and inhibition of bowel function. In the United States, chronic opioid use and abuse continues to impose a burden of morbidity, and several studies suggest that surgery, in and of itself, is a risk factor for chronic opioid use.[6] In addition, over prescription of narcotics after surgery is common given our lack of knowledge on narcotic requirements postoperatively as an outpatient, and therefore retained surplus medication often provides a readily available source of non-prescription opioids.[7]

Although minimally invasive surgical techniques aim to decrease both the visceral and non-visceral burden of pain compared to open procedures, patients still generally require narcotic and nonnarcotic analgesia following minimally invasive gynecologic surgeries (MIGS). Enhanced recovery after surgery (ERAS) pathways in gynecologic/oncology surgery have shown significant improvements in recovery time and pain control, as well as decreased narcotic demands. The emphasis of post-operative pain management is on multimodal analgesia regimens.[8] Currently, most ERAS literature for MIGS focuses on multimodal analgesia from a pharmacologic perspective, including acetaminophen, NSAIDs, gabapentin and dexamethasone.[9] Currently, non-pharmacologic methods of analgesia are not well supported in gynecologic laparoscopic surgery, and neither TAP

blocks nor intraperitoneal instillation of local anesthetic are recommended based on the current level of evidence.[9]

Non-pharmacologic cold therapy, such as ice packs or cold gel packs, is an effective form of postoperative analgesia in sports medicine, orthopedic surgery, hernia repair and maxillofacial surgery.[2,10,11,12,13] It has even been shown to improve quality of life scores post-operatively in maxillofacial surgery.[12] Cold therapy is thought to act as a local anesthetic by decreasing inflammation, reducing edema, decreasing metabolic demands, slowing nerve conduction velocity and reducing muscles spasms.[1,11,12,13] It is inexpensive, low risk and easily applicable in an outpatient setting, with very few adverse side effects.[10] Currently, ERAS literature in gynecology does not include the use of cold therapy following gynecologic/oncology surgery. Based on clinical experience, however, individual hospital protocols have incorporated cold therapy application into post-operative multimodal analgesia regimens. Watkins et al. demonstrated that the application of ice packs to vertical midline incisions postoperatively, resulted in significantly decreased post-operative pain scores and decreased need for narcotic analgesia.[1] To our knowledge, there is no literature regarding the use of cold therapy post-operatively in laparoscopic, and more specifically gynecologic, surgery.

This study aims to examine if there is a difference in post-operative pain scores with the application of cold therapy to laparoscopic abdominal incisions following laparoscopic hysterectomy, when compared to no cold therapy. Secondarily, we will examine post-operative quality of life scores, postoperative surgical recovery scores, as well as narcotic use among the two groups. We also aim to ascertain more information regarding total quantity of narcotics used post-operatively to aid in prescribing patterns.

1.2. Clinical Data to Date

Cold therapy, such as ice packs or cold gel packs, has been shown to be an effective form of postoperative analgesia, with benefits seen in sports medicine, orthopedic surgery, hernia repair, maxillofacial surgery and even after abdominal surgery.[1,2,10,11,12,13] Demonstrated benefits of cold therapy include decreased pain scores, decreased narcotic use and improved quality of life scores.[1,2,10,11,12,13] Watkins et al performed a randomized control trial demonstrating decreased postoperative pain scores and narcotic demands in patients whom applied ice packs to their abdominal incision after laparotomy, when compared with a control group.[1] There were no adverse side effects and no reports of thermal injury associated with the ice packs.[1]

1.3 Dose Rationale and Risk/Benefits

Previous studies have demonstrated that after laparoscopic gynecologic surgeries and specifically after laparoscopic hysterectomy, patients' pain scores are highest on postoperative (POD) #0-1, that many patients take narcotics through POD#3, and that most patients are off of narcotics by POD#4.[4] Since we aim to examine if cold therapy affects postoperative pain scores or narcotic use, we will instruct patients in the experimental group to use ice packs, as an adjunctive analgesic therapy for the first three days post-operatively. Literature suggests that an application time of 20-30 minutes is recommended for beneficial effect of cold therapy, while minimizing the risk of any adverse reactions from cold application.[11] We will therefore instruct patients to apply cold therapy for 20-30 minutes to abdominal incisions every 6 hours for the first three days of surgery. The 6-hour interval is to simplify dosing, as scheduled postoperative analgesic medications are also dosed every 6 hours (i.e. acetaminophen and ibuprofen). Risks of thermal injury from intermittent cold therapy are very low.[1, 10, 11, 12]

1.4 Hypothesis

Following laparoscopic hysterectomy, the prescription of cold therapy as an adjunctive analgesic agent to routine multi-modal analgesia, will decrease patients' reported postoperative pain scores.

2.0 STUDY OBJECTIVES

Primary Objective

The primary objective of the study is to evaluate postoperative pain scores following laparoscopic hysterectomy, to determine if there is a difference in pain scores with the application of cold therapy to abdominal incisions, when compared to no cold therapy in the experimental and control groups at 24 and 72 hours, respectively. The pain scores at 24 and 72 hours will be compared between the control and experimental groups.

Secondary Objectives

- To compare the amount of patient reported narcotics used for post-operative analgesia (in morphine equivalents) between the study and control groups at 24 and 72 hours after surgery.
- To compare postoperative quality of life scores between the study and control groups using the validated Abdominal Surgery Impact Scale[15] at 72 hours after surgery.
- To compare postoperative recovery scores between the study and control groups using the validated Surgical Recovery Scale (SRS)[19] 10-14 days after surgery.

Tertiary Objective

To ascertain the mean and median patient reported total amount of narcotics used post-operatively (in morphine equivalents), collected at the 10-14 day postoperative visit in all patients. This data will be collected and reported in an effort to help guide prescribing practices of narcotic medications following laparoscopic surgery.

3.0 STUDY DESIGN

3.1 General Design

The study design is a randomized controlled trial examining post-operative pain scores and outcomes after laparoscopic hysterectomy in patients prescribed cold therapy as an adjunct to routine post-operative multi-modal analgesia, compared to those patients prescribed routine multi-modal analgesia without cold therapy. All patients scheduled for total laparoscopic hysterectomy (without robotic-assistance) will be screened for eligibility in the study. If eligible, patients will be invited to participate in the study and standardized informed consent process will ensue.

All research activities will commence on the day of surgery, in the preoperative preparation area. Enrolled subjects will undergo standard registration and preoperative preparation by the staff preoperative nurse, including placement of intravenous access line and administration of standard routine preoperative medications. Preoperative medications (unless contraindicated due to patient allergy) include single dose prophylactic antibiotics given prior to surgical incision, Dexamethasone 10mg IV (unless the patient is diabetic), Ondansetron 4mg IV and Gabapentin 600mg PO given in the preoperative preparation area.[20, 21] Patients with a preoperative Caprini score of 5 of greater will also receive Heparin 5000 units subcutaneous, for DVT prophylaxis. Deviation from standard preoperative medications will be recorded. While in the pre-operative area, and prior to any sedative drug administration by anesthesia, the patient will complete an 11-point Numeric Rating Scale (NRS) to record baseline pain, as well as a baseline 18-question quality of life survey with the Abdominal Surgery Impact Scale (ASIS). Both study instruments will be self-administered by the patients and collected by the research team.

The patient will then be moved to the operating room. Induction, intubation and anesthesia administration will be performed according to standard practice by a dedicated group of anesthesia providers. Anesthesia providers familiar with the protocol will administer anesthesia per routine practice, using short acting agents to allow for rapid awakening and lung protective ventilation (tidal volumes of 5-7ml/kg with a PEEP of 4-6cm H20) whenever possible or unless contraindicated.[20] Prior to surgical incision, preoperative prophylactic antibiotics will be administered. The patient will be positioned in the dorsal lithotomy position with bilateral upper extremities in a tucked position. Surgical sterile preparation and draping will be performed per usual technique.

Laparoscopic entry will typically be obtained by 5mm optical trocar in the periumbilical region, but placement may be modified at the surgeon's discretion. Pneumoperitoneum will be established through this trocar to 15mmHg. Three additional laparoscopic trocars will be placed in one of two configurations, as per primary surgeon preference accounting for size of uterine pathology. The skin and subcutaneous tissue will be infiltrated with 1% lidocaine with epinephrine for local anesthetic prior to all skin incisions and port placement. The patient will be placed in Trendelenburg position and the surgery will be performed and completed in typical fashion. Upon conclusion of the procedure total operative time, estimated blood loss (EBL), total skin incision number and cumulative incision length will be recorded. If a mini-laparotomy was created for transabdominal tissue extraction, incision location and length will also be recorded. All skin incisions will be closed in a subcuticular fashion and sealed with skin adhesive.

Randomization will occur after the patient's last skin incision is dressed with skin adhesive, indicating conclusion of the procedure. If randomized to the experimental group, cold gel pack(s) will be placed over the patient's abdominal incisions prior to leaving the operating room. If randomized to the control group, no additional treatment will take place outside of routine postoperative monitoring and management.

The patient will emerge from anesthesia under routine monitoring and will be transferred to the post-anesthesia care unit (PACU) when meeting appropriate criteria per anesthesia discretion. A staff PACU nurse will care for the patient in the PACU and administer one dose of Toradol 30mg IV, as well as narcotic medications as necessary and/or per patient request. All pain medications administered in the hospital will be recorded in the Epic electronic health record (EHR). The amount of each patient's narcotic administration will be recorded from the EHR and documented in study files. We are unable to blind the staff PACU nurse to patient group allocation given the nature of the intervention. All patients will remain in PACU until meeting PACU discharge criteria and will be discharged to home on POD#0 with postoperative instructions for analgesic medications and cold therapy if applicable. If patients are unable to be discharged home, they will stay overnight in the hospital with documented rationale.

All patients will be discharged home with uniform medication prescriptions as well as a daily Pain Score and Intervention Log (PSIL) to document medication/intervention use. All patients will receive written instructions for medication use (see attached). The experimental group will also receive written instructions for scheduled cold therapy use, to be used concomitantly with scheduled analgesics, as indicated below. All patients will be discharged home with prescriptions for Ondansetron 4mg PO every 8 hours as needed for nausea/vomiting (quantity 12), Colace 100mg PO twice daily (quantity 60), scheduled Ibuprofen 600mg PO every 6 hours (quantity 30), scheduled acetaminophen 650mg PO every 6 hours (quantity 30), and oxycodone 5mg PO every 4 hours as needed for breakthrough pain (quantity 30). The experimental group will also receive reusable cold gel packs with instructions to apply cold therapy to abdominal incisions every 6 hours for 20-30 minutes

through POD#3. The rational for cold pack use through POD#3 is that most patients are off of narcotic pain medications by POD#4[4]. Scheduled ibuprofen and acetaminophen dosing is based on literature supporting that acetaminophen and ibuprofen should be used together[16], and that clinicians should routinely incorporate around-the-clock non-opioid analgesics and non-pharmacologic therapies into multimodal analgesia regimens[5].

Approximately 24 hours after surgery, the patient will be contacted by a research team member who will administer an NRS pain survey via telephone and ask patient to report total number of narcotic pills used since discharge. If patient is still in the hospital, narcotic usage will be obtained from the EHR.

Approximately 72 hours after surgery, the patient will be contacted by a research team member who will administer an NRS pain survey, an ASIS quality of life via telephone. Patient will again be asked to report total number of narcotic pills use since discharge.

Per standard routine care, the patient will be asked to return to clinic 10-14 days after surgery for evaluation and examination. Patients will be asked to turn in PSIL at this visit. They will also be asked to complete a Surgical Recovery Scale (SRS). They will be asked to bring their narcotic prescription bottle to count the total number of narcotic pills remaining at the time of their two week visit. They will be asked if they are still taking the narcotic medication. If patients received a refill for narcotic medications prior to postoperative visit, counts will occur in the same manner accounting for additional pills, and it will be recorded in study data. The patient will exit the study after this visit.

3.2 Primary Study Endpoints

The primary objective of the study is to evaluate postoperative pain scores on a validated 11 point NRS[14] at 24 and 72 hours for patients who have undergone laparoscopic hysterectomy. Pain scores at 24 and 72 hours will be compared between the control group and the experimental group. The 11-point NRS scale consists of whole number responses from zero (0) to ten (10). The NRS scale will be used versus a visual analog scale (VAS) as it can also be administered by telephone (important to secondary endpoints).

3.3 Secondary Study Endpoints

1. As pain scores from the NRS may represent controlled or uncontrolled pain, total narcotic usage will also be collected at 24 and 72 hours. Narcotic usage will be tracked by patient using their PSIL, and reported by patient during follow-up phone call. Patients will be asked to provide the total number of narcotic pills remaining in their bottle. Amount of narcotic usage will be converted to intravenous morphine equivalents for comparison purposes. The patient reported values will be compared with their PSIL when turned in at their post-operative visit.
2. Quality of life will be measured with the Abdominal Surgery Impact Scale (ASIS). It covers six domains including physical limitations, functional impairment, pain, visceral function, sleep, and psychological function. Three items in each domain create a total of 18 items, and this instrument has been previously validated[15] with its design for use in open or laparoscopic abdominal surgery in determining health-related post-operative quality of life. Subject responses to each item are on a seven-point Likert scale ranging

from 1 to 7. The possible total score ranges from 18 to 126, with higher scores reflecting improved quality of life. Patients are instructed to respond based on their feelings for the immediately preceding 24 hours. This instrument will be self-administered in the pre-operative area the day of surgery, and again at 72 hours post-operatively by the research team via a telephone call.

3. Postoperative recovery scores will be measured using the Surgical Recovery Score (SRS).[19] The aim of the tool is to reliably measure functional patient recovery following surgery. It provides an outcomes measure against which interventions used to enhance recovery can be assessed, and this instrument has been previously validated[19] with its design for use in open or laparoscopic abdominal surgery. There are 13 SRS items, all of which are scored from 0 to 5, or 0 to 4, with total scores ranging from 0 to 60, with higher scores indicating better recovery. Patients are instructed to respond based on their feelings for the preceding two days. The instrument with be administered by the research team at their 10-14 day post-operative visit.

4. Total narcotics used postoperatively will be measured at the 10-14 day postoperative visit. Patients will be asked to bring their narcotic pill bottle to their post-operative visit. Total narcotic pill use will be calculated by counting the number of pills remaining in their bottle and compared with their PSIL. Total narcotic usage will be converted to intravenous morphine equivalents for comparison purposes. This data will be collected and reported in an effort to help guide prescribing practices for narcotic medications following laparoscopic surgery.

3.4 Primary Safety Endpoints

All complications including but not limited to vascular, bladder, ureter, and intestinal injury, need for blood transfusion, venous thromboembolism, or other cardiac and respiratory complications within the first 30 days after surgery will be recorded. Total procedure time and estimated blood loss will also be recorded throughout the study. Any adverse events related to cold therapy use will be documented and reported, and in the event of severe adverse reactions will be treated appropriately and cold therapy will be immediately stopped in that patient.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for study enrollment:

1. Patients can understand and voluntarily sign an informed consent form
2. Female gender ages 18-65
3. Scheduled for laparoscopic hysterectomy for benign indications, total or subtotal, without or without oophorectomy (standard of care involves bilateral salpingectomy)

4.2 Exclusion Criteria

Meeting any of the following exclusion criteria will make the subject ineligible for study enrollment:

1. Conversion to laparotomy
2. Diagnosis of chronic pelvic pain

3. No access to freezer at home to keep reusable cold packs cold between uses
4. Contraindications to exposure to cold therapy (history of cold allergy, cold intolerance, Raynaud's disease, cold urticaria, cryoglobulinemia, or pyoderma gangrenosum)
5. Medical contraindication to NSAID use

4.3 Subject Recruitment and Screening

All patients scheduled for laparoscopic hysterectomy are typically seen in clinic within 30 days of surgery for a pre-operative appointment. If meeting inclusion criteria, they will be introduced to the study by a member of the research team in the clinic room following their appointment. Confirmation will be made by the research team that the patient does not have a previous diagnosis of chronic pelvic pain, that the patient has access to a freezer postoperatively, that the patient has no contraindications to exposure to cold therapy and that the patient has no medical contraindication to NSAID use. If agreeable to participation, an informed consent form will be signed that day. If unable to discuss the study during the pre-operative appointment, a member of the research team will call the patient by telephone to introduce them to and discuss the study. If the patient is agreeable to enrollment verbal consent and conversation will be documented in the EHR, and the informed consent document will be signed the day of surgery, after again reviewing the risks and benefits of the study.

4.4 Early Withdrawal of Subjects

Patients may withdraw from the trial at any time and for any reason. Some possible reasons for early withdrawal include the following:

- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial (such as surgery for other indications or trauma)
- Unacceptable toxicity or any adverse event that precludes further participation in the trial
- The investigator removes the patient from the trial in the best interests of the patient
- Study completion or discontinuation
- Patient withdraws consent to continued participation in the trial
- If the procedure cannot be completed by laparoscopy and is converted to laparotomy, patient will be removed from the study by the research team, prior to randomization

4.5 Data Collection and Follow Up for Withdrawn Subjects

As above, subjects may withdraw at any time, or for above listed conditions. Subjects may choose if any data collected prior to withdrawal can be used in data analysis. If withdrawn subjects do not want data included in analysis, it will be discarded safely. Follow-up will consist of standard care with post-operative clinic visits at 10-14 days and 6 weeks. If patients withdraw after surgery, we will ask to review their chart for morbidity or mortality within 30 days of surgery.

5.0 STUDY DRUG (or Device, Biologic, Treatment)

5.1 Description

The study intervention is cold therapy administered via reusable cold gel packs. The intervention is not experimental. Cold therapy has been shown to be an effective form of postoperative analgesia, it just has not been evaluated after laparoscopy, to the best of our knowledge.[1,2,10,11,12,13]

5.2 Treatment Regimen

Previous studies have demonstrated that after laparoscopic gynecologic surgeries and specifically after laparoscopic hysterectomy, patients' pain scores are highest on postoperative days(POD) 0-1, that many patients take narcotics through POD#3, and that most patients are off of narcotics by POD#4.[4] Since we aim to examine if cold therapy affects postoperative pain scores or narcotic use, we will instruct patients in the experimental group to use ice packs, as an adjunctive analgesic therapy for the first three days post-operatively. Literature suggests that an application time of 20-30 minutes is recommended for beneficial effect of cold therapy, while minimizing the risk of any adverse reactions from cold application.[11] We will therefore instruct patients to apply cold therapy for 20-30 minutes to abdominal incisions every 6 hours for the first three days of surgery. The 6-hour interval is to simplify dosing, as scheduled postoperative analgesic medications are also dosed every 6 hours (i.e. acetaminophen and ibuprofen). Patients may use the cold therapy more frequently if desired. Risks of thermal injury from intermittent cold therapy are very low.[1, 10, 11, 12] Previous studies have resulted in no adverse side effects and no reports of thermal injury associated with cold packs applied to the abdomen postoperatively.[1]

5.3 Method for Assigning Subjects to Treatment Regimen

Subjects will be assigned a sequential research ID number at time of enrollment (in clinic or by telephone). A randomized list will be created in blocks of 4 and 6 with Sealed Envelope (Sealed Envelope Ltd. 2015. Simple randomization service. Available from: https://www.sealedenvelope.com/simple-randomiser/v1/). Group assignment will be written on a card and placed in a numbered (corresponding to research ID number), opaque envelope. Envelopes will be opened by the research team in the operating room at the conclusion of the operation to reveal randomization. Randomization will be stratified to include equal numbers of patients with and without mini-laparotomy incisions enrolled in both the treatment and control group. Patients with pre-operative uterine size measuring 16 weeks or greater in size will be presumed to require a mini-laparotomy incision for tissue extraction. This is generally routine practice within our group for tissue extraction. If however mini-laparotomy is not required surgically, and we are able to remove the specimen vaginally, the randomization stratification will not change. This will be in an effort to maintain equal number of patients undergoing mini-laparotomy or not, in both the control and treatment group.

5.4 Preparation and Administration of Study Treatment

After randomization, the study group participants will receive cold gel pack(s) to be applied to abdominal incisions beginning either in the operating room or no later than while the patient is in the PACU. They will also receive additional written instructions on cold therapy use as previously described (please see attached documents for written patient instructions). The cold therapy packs will be kept cold in a designated freezer to be readily available postoperatively. The cold gel pack and written instructions will be delivered by a research team member to patients randomized to the study group. Patients will be instructed to call primary co-investigator immediately should patients experience any adverse side effects or event related to the cold therapy and to discontinue use of cold therapy until addressed by research team member. All such instances will be recorded in research data.

5.5 Subject Compliance Monitoring

Subject compliance will be tracked using the PSIL that will be provided to all patients on POD#0 prior to discharge to home (please see attached). Patients will receive written instructions for

recording cold therapy use as well as medication use and pain scores. Patients using cold therapy will be considered compliant if they use the cold therapy intervention at least 75% of the suggested time, which includes every 6 hours for the first 72 hours. This compliance will be recorded and reported as necessary.

5.6 Prior and Concomitant Therapy

Patients in both the control and experimental group will receive concomitant medical therapy by means of routine postoperative analgesia as described above in section 3.1. All patients will be discharged home with uniform medication prescriptions as well as a daily Pain Score and Intervention Log (PSIL) to document medication/intervention use. All patients will receive written instructions for medication use (see attached). All patients will be discharged home with prescriptions for Ondansetron 4mg PO every 8 hours as needed for nausea/vomiting (quantity 12), Colace 100mg PO twice daily (quantity 60), scheduled Ibuprofen 600mg PO every 6 hours (quantity 30), scheduled acetaminophen 650mg PO every 6 hours (quantity 30), and oxycodone 5mg PO every 4 hours as needed for breakthrough pain (quantity 30). Scheduled ibuprofen and acetaminophen dosing is based on literature supporting that acetaminophen and ibuprofen should be used together[16], and that clinicians should routinely incorporate around-the-clock non-opioid analgesics and non-pharmacologic therapies into multimodal analgesia regimens[5]. Use of the above concomitant medications will be documented in the PSIL administered to all patients, specific to their randomization group. Control group patients will be requested to not use cold therapy as it is not a routinely recommended intervention and is the study intervention.

5.7 Blinding of Study Drug (Device or Treatment)

We are unable to blind the study participants given the nature of the intervention.

6.0 STUDY PROCEDURES

6.1 Pre-registration and Screening

This will occur at the pre-operative clinic appointment within 30 days of surgery, or by telephone call prior to, but within 30 days of surgery. Screening will occur to ensure patient meets all inclusion criteria and no exclusion criteria. Informed consent signing will occur at this clinic visit, or the day of surgery if enrolled verbally by telephone.

6.2 Pre-operative, Day of Surgery

Patient will undergo routine registration and surgical readiness by a staff pre-operative nurse. The research team assistant will administer an NRS pain survey and an ASIS quality of life survey.

6.3 Intra-operative, Day of Surgery

The subject will undergo laparoscopic hysterectomy according to standard routine. After completion of the surgical procedure, randomization will occur. If randomized to the experimental group, cold therapy will be initiated either in the operating room or no later than upon arrival to PACU. Surgical data will also be collected as described in section 3.1.

6.4 24 Hours Post-operatively

A research team member or research assistant will contact the patient 24 hours after surgery by telephone (or in person if patient is still hospitalized). An NRS pain survey will be administered by the team member or assistant, who will also record responses on the reporting form. Subjects will also be asked to report number of narcotic pills used since discharge and associated dosages.

6.5 72 Hours Post-operatively

A research team member or assistant will contact the patient 72 hours after surgery by telephone (or in person if patient is still hospitalized). An NRS pain survey and an ASIS quality of life survey will be administered by the research team member or assistant, who will also record responses on the designated reporting forms. Subjects will also be asked to report number of narcotic pills used since discharge and associated dosages.

6.6 10-14 Day Post-operative Visit

Standard evaluation and examination will occur at this visit. The research team member or assistant will collect the patient's PSIL as well as count and record the total number of narcotic pills remaining in the patient's pill bottle. It will be recorded if the patient is still taking the narcotic pain medication. It will also be recorded if the patient has required a refill of narcotic medication prior to post-operative visit. The patient will also be asked to complete a Surgical Recovery Scale (SRS) survey.

6.7 Study Calendar of Procedures

	Pre-Study	Pre-Op	Intra-Op	24 hrs Post-Op (Phone)	72 hrs Post-Op (Phone)	10-14d Post-Op (Clinic)
ENROLLMENT	**X**					
INFORMED CONSENT	**X**					
DEMOGRAPHICS	**X**					
MEDICAL HX	**X**	**X**				**X**
PHYSICAL EXAM	**X**	**X**				**X**
PAIN NRS SURVEY		**X**		**X**	**X**	
ASIS QoL SURVEY		**X**			**X**	
RANDOMIZATION			**X**			
NARCOTIC DATA				**X**	**X**	**X**
SRS SURVEY						**X**
COLLECT PSIL						**X**

- Pre- study evaluations must be performed within 30 days of surgical procedure.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

Although cold therapy has been found to be effective in other post-operative patient populations and in other medical settings, such as sports medicine, there is no previous literature, to the best of our knowledge, evaluating the use of cold therapy after laparoscopic surgery. For this reason we plan to perform a pilot study for initial determination of a statistical difference in post-operative pain outcomes. We plan to enroll 28 patients in each arm, stratified to 14 patients with mini-laparotomy incisions and 14 patients without mini-laparotomy incisions, for a total of 56 patients. 56 patients will allow the pilot study to be completed in a reasonable time frame.

7.2 Statistical Methods

After all data has been collected, demographic, preoperative and intraoperative data will be summarized overall and by randomized group, using frequencies and percentages for categorical factors, and means and standard deviations for continuous measures. Primary outcome data will be analyzed using Mann-Whitney test for continuous nonparametric data. Secondary continuous outcomes data will analyzed using means and an unpaired t-test. Tertiary outcome data will simply be recorded and reported. All data collected will be recorded and stored in RedCap.

7.3 Subject Population(s) for Analysis

The all-treated population will be used for data analysis for primary, secondary and tertiary objectives. Inter-group analyses will occur as listed in the primary objective (Section 2.0).

If patients are not able to be contacted for the 24 hour or 72 hour post-operative phone call assessments, or 10-14 day post-operative visit, they will not be included in analyses of these data alone.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

An adverse event (AE) is any untoward or unfavorable medical occurrence, symptom, disease, abnormal physical exam finding, or abnormal laboratory result which occurs to a participant in research conducted by Cleveland Clinic Florida. Psychological harms also constitute adverse events.

A serious adverse event (SAE) is an adverse experience that results in any of the following outcomes:

- Death
- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability / incapacity.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will also be recorded in the source document.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) will be submitted to the CCF IRB per guidelines in the CCF IRB Standard Operating Procedures manual. The following four types of events will be reported to the IRB:

1. Adverse events which are serious, unexpected, and related or possibly related to participation in the research.
2. Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.
3. Other unexpected adverse events, regardless of severity, that may alter IRB analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.
4. Unanticipated Problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB.

8.4 Stopping Rules

An interim analysis of the patient data will be performed when 50% of the patients have completed the study. If a statistically significant proportion of patients have had adverse reactions or serious adverse reactions due to the study intervention of cold therapy, the study will halt. If any adverse outcome is fatal, the study will immediately halt and the IRB will be notified. In the case that the study is stopped then the IRB will be notified.

8.5 Medical Monitoring

The Principal Investigator with the research team will hold responsibility for monitoring of post-operative complications. As the research intervention only involves application of cold therapy to abdominal incisions, only potential adverse effects of cold therapy are expected as compared to the control group. Careful monitoring for adverse events will occur with assurance that reporting follows the above guidelines. The number and type of adverse events will be recorded in the case report forms. Diligence will be maintained to observe for any known complication of laparoscopic hysterectomy in all patients. Any SAE will be reported to the IRB as listed above in section 8.3.1.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality and Privacy

Information about study subjects will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). An informed consent document will be signed by all patients prior to surgery and will list

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke authorization for use of PHI.

Only the enrollment log will contain identifiable personal health information including the patient's name and assigned research identification number. This will be kept on a secure Cleveland Clinic Florida drive, and a paper copy will be kept in a locked filing drawer in the research team's office on the Cleveland Clinic Florida property. The CRFs will only contain research identification numbers without protected health information. These will also be kept in a locked file. The data from the CRFs will be entered online into a RedCap database by a member of the research team. Only members of this research team will have access to this information.

9.2 Source Documents

Source data will include the electronic health record for patient demographics, history and physical exams, operative notes, progress notes from post-operative visits, anesthesia records, vitals, and events related to the surgery. Pertinent information will be pulled from the electronic health record onto the CRFs. The questionnaires completed by patients will be kept in a locked filing drawer in the research team's office on the Cleveland Clinic Florida property.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documentation. Examples include but are not limited to: original documents, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, copies or transcriptions of electronic records certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratories, etc.

9.3 Case Report Forms

The attached case report form will have spaces for documentation of demographics, baseline pain scores and survey results, surgical data, post-operative pain scores and survey results, and post-operative narcotic use. The ASIS and SRS survey will be kept as an appendix to the CRF for each patient. This data will be transcribed to a secure RedCap database for analysis by a member of the research team.

9.4 Records Retention

Data within the EHR will exist in its perpetuity, as will the secure files on the Cleveland Clinic server (at least 6 years after study completion). All consent documents, case report forms, and QOL surveys will be maintained in a secure file cabinet within the Department of Gynecology at Cleveland Clinic Florida for at least 6 years.

10.0 STUDY MONITORING, AUDITING AND INSPECTING

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and Institutional compliance and quality assurance groups of all study related documents (for example, source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Institutional compliance and quality assurance offices.

11.0 ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator prior to commencement of the study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision.

12.0 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the study investigators. The investigators alone hold responsibility for publication of study data and results.

13.0 REFERENCES

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14.0 ATTACHMENTS

- Feasibility Checklist
- Informed Consent Form
- Case Report Form
- Abdominal Surgery Impact Scale
- Surgical Recovery Scale
- Pain Score and Intervention Log
- Postoperative Instructions for Control Group
- Postoperative Instructions for Study Group