ADMINISTRATIVE INFORMATION

I. **Title:** Superior hypogastric plexus block for postoperative pain following laparoscopic hysterectomy: a randomized controlled trial

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V. **Roles and responsibilities:**

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INTRODUCTION

VI. Background and rationale:

Postoperative pain control is an area of active investigation as inadequate pain management can lead to an increased length of stay, readmission, chronic pain, and opioid dependence.[1-3] For laparoscopic hysterectomy, several non-opioid alternatives to pain management have been evaluated in an attempt to reduce patients' pain and minimize opioid consumption. These include local anesthetics, transversus abdominis plane blocks, anticonvulsants, non-steroidal anti-inflammatory medications, and steroids. Non-opioid pain management techniques have demonstrated varying success, with a few methods providing short-term improvements in patients' pain as well as opioid-sparing benefits.[4] Superior hypogastric plexus block (SHPB) or presacral nerve block is another method that has shown promising results in patients undergoing abdominal hysterectomy; however, has not been evaluated in patients undergoing laparoscopic hysterectomy.

The superior hypogastric plexus lies in the presacral space and supplies autonomic innervation to the pelvis. This plexus has been implicated in chronic pelvic pain with studies demonstrating reduced pain scores and opioid use following image-guided percutaneous blockade or surgical transection of the plexus.[5-9] To our knowledge, only one study has investigated the efficacy of a SHPB at the time of hysterectomy.[10] This study was a double-blind randomized controlled trial of 68 women undergoing an abdominal hysterectomy, randomized to a presacral injection of 20 mL of ropivacaine versus saline. Sixty-three percent of women in the ropivacaine group had a VAS pain score less than 4 at two hours postoperatively, compared to 25% in the placebo group ($p=0.015$). Median opioid consumption was also less at 55.8 mg for the treatment group versus 72.4 mg for the placebo group ($p=0.032$). There were no side effects or adverse events reported in this study. We hypothesize that a SHPB will provide similar benefits in patients undergoing a laparoscopic hysterectomy.

VII. Objectives:

The objective of this study is to assess the efficacy of a SHPB for pain relief following laparoscopic hysterectomy. The superior hypogastric plexus lies in the presacral space and supplies autonomic innervation to the central pelvis. This plexus is suspected to play a role in postoperative pain following a hysterectomy. We hypothesize that a SHPB using the anesthetic bupivacaine will reduce patients' pain scores and opioid consumption following a laparoscopic hysterectomy.

VIII. Trial design:

This study is designed as a multi-center, randomized, single-blind, controlled trial of patients scheduled for a laparoscopic hysterectomy. Patients will be randomized to two groups: one group will receive a SHBP and laparoscopic hysterectomy, and the other will receive no block and laparoscopic hysterectomy.

METHODS

IX. Study setting:

The study will be conducted at three sites: Brigham and Women's Hospital (BWH)/Brigham and Women's Faulkner Hospital(FH), University of North Carolina Medical Center (UNC) and George Washington University (GWU).

X. Eligibility criteria:

Patients over 18 years of age who are scheduled for a laparoscopic hysterectomy at participating sites will be recruited to participate. Patients of all comorbidities will be eligible for inclusion; specifically, patients with chronic pain syndromes will not be excluded so as to evaluate the efficacy of SHPB in this population. The exclusion criteria include patients who are unwilling to consent, who have an allergy to block medications used in the trial, are undergoing a sacrocervicopexy or a sacrocolpopexy, are undergoing a laparotomy, or those with anatomy that limits the safe application of a presacral injection (per the surgeon's discretion at the time of the procedure). Patients will not be excluded if they undergo other concomitant procedures during laparoscopic hysterectomy. While concomitant procedures may contribute to patients' pain following laparoscopic hysterectomy, this will improve the external validity of the trial. Moreover, randomization should balance differences in patients and procedures between the two treatment arms.

XI. Interventions:

If the patient is randomized to a SHPB, it will be performed laparoscopically by the gynecologic surgeon at the start of the hysterectomy procedure. The SHPB block will contain 10 mL of 0.25% bupivacaine hydrochloride (2.5 mg/mL = 25 mg). The injection will be performed by tenting the presacral peritoneum, aspirating with a laparoscopic needle-tip syringe to ensure extravascular placement, and injecting the block with the laparoscopic needle-tip syringe (Appendix XXXIV). Patients in the control arm will undergo the planned procedure with no intervention. Following the procedure and intervention, surgeons will be

asked to complete a worksheet to assess the feasibility and safety of presacral injection, as well as details regarding the procedure (Appendix "SHPB MD Worksheet").

All participants will undergo a surgically-indicated laparoscopic hysterectomy as planned. As per routine practice, all patients will also receive an incisional anesthetic using 20 mL of 0.25% bupivacaine at the laparoscopic port sites. Patients in the intervention group will additionally undergo a SHPB (10 mL of 0.25% bupivacaine laparoscopically injected in the presacral space) at the start of the procedure. The surgical risks of a SHPB are similar to any surgical procedure and include bleeding, infection, and injury to surrounding vessels and organs. These risks are expected to be very rare as all participating surgeons are expert laparoscopists who have safely operated in the presacral space. Viewing a video demonstrating this technique will also be required of all participating surgeons prior to the study. If a patient's anatomy or pathology prohibits the safe application of a SHPB then the intervention will be abandoned.

All surgeons who will enroll patients from BWH, FH, UNC and GWU are experienced laparoscopic surgeons who have performed at least 100 advanced laparoscopic procedures including hysterectomy. Laparoscopic hysterectomy will be performed by the participating surgeons in the usual fashion, with inherent operator-dependent variation in technique. All participating surgeons will be required to view a video describing the technique of SHPB to ensure the procedure is performed similarly in all patients.

In an effort to reduce external factors that may influence postoperative pain, patients will be standardized to similar preoperative and postoperative medications. The standard preoperative medication regimen will include Celecoxib 200 mg po, Tylenol 975 mg po and Gabapentin 900 mg po. Patients will also receive the standard incisional anesthetic with 20 mL of 0.25% bupivacaine hydrochloride (2.5 mg/mL = 50 mg, combined with block totals 75 mg, max dose 2mg/kg therefore safe in all patients with weight over 37.5 kg). Patients will receive intraoperative narcotics at the discretion of the anesthesia team. Intraoperative narcotic use will be collected from the medical record.

The standard postoperative medication will include Toradol 30 mg IV unless a patient is 65 years of age or older or has renal or vascular disease. All patients will also receive a prescription for 20 tablets of Oxycodone 5 mg po (or 20 tablets of Hydrocodone 5 mg po or 20 tablets of Hydromorphine 2 mg po, in the event of an allergy/intolerance to Oxycodone). Note will be made of any refills during the eight-week recovery period. Patients will be provided postoperative narcotics in the recovery unit as needed per anesthesia and nursing assessment. If a patient has an allergy to any of the pre or postoperative medications, they will not receive that medication.

The block will contain 10 mL 0.25% bupivacaine hydrochloride. Bupivacaine hydrochloride is a long-acting anesthetic that is FDA-approved for local anesthesia (subcutaneous) and is routinely used at the time of laparoscopic surgery (see attached FDA approval letter and labeling). Adverse effects of bupivacaine are rare and often dose-related. Adverse effects include nausea/vomiting, anxiety, dizziness, blurred vision, and tinnitus. Toxicity can result in bradycardia, hypotension, arrhythmia, hypoventilation, apnea, and cardiac arrest. The presacral block will contain 25 mg of bupivacaine (10 mL of 0.25% bupivacaine, 2.5 mg/mL)

and the incisional block will contain 50 mg of bupivacaine (20 mL of 0.25% bupivacaine, 2.5 mg/mL) for a total dose of 75 mg. The maximum safe dose of bupivacaine is 2 mg/kg therefore all patients with a weight over 37.5 kg (82.5 lbs) will be safe to receive this dose. This weight threshold encompasses nearly all women over age 18. In the very unlikely event that a patient weighs less than this, the incisional block will be reduced accordingly. No additional bupivacaine will be used during the procedure. Patients with an allergy to bupivacaine will be excluded from the study.

Patients will be charged for the bupivacaine anesthetic as it is a standard component of a laparoscopic hysterectomy and is routinely injected in the incisions for local anesthesia. All patients will be receiving the anesthetic in the incisions regardless of the treatment arm. Only patients in the SHPB arm will also receive the anesthetic in the presacral space. This is not anticipated to add cost to the procedure as all patient in the study will receive this medication.

XII. Outcomes:

The primary outcome will be immediate postoperative patient pain scores (within 4 hours) using the Visual Analog Scale (VAS) in the recovery unit. The secondary outcomes will be intraoperative and postoperative opioid consumption as well as VAS pain scores from the Brief Pain Inventory (BPI) as recorded in a patient diary for one week following surgery. Subgroup analyses will be performed on patients undergoing a hysterectomy for pelvic pain and patients who undergo a laparoscopic hysterectomy without concomitant procedures.

XIII. Participant timeline:

Participation starts with enrollment and an eligibility screen. Eligible patients who agree to participate will be consented on the day of surgery. Patients will undergo surgery and be followed up to eight weeks postoperatively.

XIV. Sample size:

A sample size was determined using prior data on the increased percentage of patients with low VAS scores following SHPB and abdominal hysterectomy.[10] Sixty-three percent of women in the ropivacaine group had a VAS pain score less than 4 at two hours postoperatively, compared to 25% in the placebo group ($p=0.015$). A two-sample comparison of proportions with a beta error of 0.2, alpha error of 0.05, and 10% loss to follow-up, therefore requires a sample size of 58 patients. Accounting for heterogeneity in the patient population we aim to recruit 100 patients, with 50 in each treatment arm. Patients will be enrolled at BWH, FH, UNC and GWU, with approximately 50 patients coming from BWH/FH, 30 patients from UNC and 20 patients from GWU. We expect to enroll approximately 20 patients per month between the three sites. Data collection is anticipated to take approximately seven months, accounting for postoperative evaluation up to eight weeks after surgery.

XV. Recruitment:

Recruitment begins at the initial consult visit. The surgeon will explain the study, and then ask the patient if they would like to hear more about it. Only patients that affirm that they are

interested will then be given a description of the study protocol and a copy of the consent form to take home with them (Appendix "SHPB Consent Form"). If a subject decides they do not want to participate, a decline card will be included in the materials. A research assistant will also contact subjects by phone to answer any questions regarding the study. Patients who remain interested in participating will be formally consented on the day of surgery by one of the participating surgeons.

XVI. Assignment of interventions, allocation concealment, and implementation:

Patients will be randomized on the day of surgery after informed consent has been obtained. Subjects will be randomized using urn randomization with a 1:1 allocation of treatment and placebo, stratified by the three sites (BWH/FH, UNC and GWU). Randomized allocation of the treatment arms will be concealed in sequentially-numbered, opaque, sealed envelopes. The randomization sequence and concealed allocation envelopes will be prepared by a research assistant and unknown to the remainder of the study staff.

Patients will be randomized to two treatment groups: one group will receive the SHPB, and the other will receive no block. Patients will be randomized after informed consent is confirmed on the day of surgery. Subjects will be randomized using urn randomization with a 1:1 allocation of treatment and placebo, stratified by the three sites (BWH/FH, UNC and GWU). Randomized allocation of the treatment arms will be concealed in sequentially-numbered, opaque, sealed envelopes. The randomization sequence and concealed allocation envelopes will be prepared by a research assistant and unknown to the remainder of the study staff. A placebo arm (e.g. presacral injection of saline) was not designated given little to no anticipated benefit of a sham block. For the treatment arm, the risks of presacral injection are anticipated to be very rare and superseded by the potential benefit of reduced postoperative pain as demonstrated in patients undergoing abdominal hysterectomy.[10]

XVII. Blinding:

Patients will be blinded to the treatment arm; however, the surgeon and operating room staff will know if a patient has been randomized to receive the block during the hysterectomy. Nurses in the recovery unit and on the inpatient floors will also be blinded to the treatment arm. The Medication Administration Record will document a blinded medication for patients in the trial to reduce the risk that staff caring for patients outside the operating room become aware of the treatment arms.

XVIII. Data collection methods:

Postoperative pain scores will be collected by a registered nurse upon admission to the recovery unit, and at every hour for four hours or until the patient is discharged. Most patients are discharged home on the same day as surgery with a recovery unit stay between two to six hours depending on the patient. If a patient is admitted to the hospital, the worksheet will be completed by the recovery unit nurse for as long as the patient is in the recovery unit and completed by the floor nurse for a total of four hours postoperatively. Pain scores will be

collected using the Visual Analog Scale to ask patients their pain level on a scale of 0 to 10, where 0 indicates no pain and 10 indicates the worst pain imaginable.

Intraoperative and immediate postoperative opioid consumption will be collected from the Medication Administration Record. The nursing staff will also be asked to complete a recovery worksheet that details the VAS pain score and opioid administration on admission to the recovery unit and every postoperative hour until four hours or the patient is discharged (Appendix "SHPB RN Worksheet"). The nursing staff will also be asked to note the total time the patient was in the recovery unit. Patients will also be asked to complete a daily diary for one week following the procedure, which details their pain level and daily opioid consumption (Appendix "SHPB Patient Diary").

Patients will be followed for eight weeks after surgery to assess for the occurrence of any postoperative complications. Detailed patient and procedure characteristics including age, race, body mass index, parity, surgical history, surgery indication, procedure type, and surgical approach will also be collected.

No additional follow-up visits will be required; however, the patient will be asked to return their postoperative diary at their routine postoperative visit (approximately four weeks after surgery). To avoid loss to follow-up, patients will be contacted one to three days after surgery or discharge to remind them to complete the daily diary for one week postoperatively. Patients who have a prolonged hospital stay or who are readmitted to the hospital during the first postoperative week will be reminded to complete the diary as an inpatient, and their narcotic consumption obtained from the medical record. Patients who do not schedule a routine postoperative visit or who forget to bring the diary to their postoperative visit will be contacted by phone or mail and a stamped and addressed envelope sent to their home address for them to return the diary.

XIX. Data management:

All healthcare personnel involved in this study will be responsible for completing correct operative and postoperative data. Patients will be asked to complete a daily postoperative diary which they will return at their postoperative visit. All other data points will be abstracted from patient medical records by research assistants. A minimum number of persons will be involved with the data abstraction in an attempt to decrease introduction of bias. The research assistants will also keep a copy of all source documents such as informed consent on file. All data will be kept in password-protected computer systems, locked file cabinets, and offices accessible only to study staff.

XX. Statistical methods:

Statistical analysis will be performed to test the null hypothesis that there is no difference in VAS pain scores or opioid consumption following laparoscopic hysterectomy with and without a SHPB. The primary analysis will be intention to treat, i.e. those patients randomized to the two treatment arms regardless of the intervention or outcome assessment. The primary outcome (immediate postoperative VAS pain scores in the recovery unit for four hours) will

be treated as continuous as well as dichotomized variables and compared using Student's t-tests if continuous and normally distributed, Wilcoxon tests if continuous and non-normally distributed, and Chi-square tests if dichotomized. A linear regression will be performed to adjust for the two participating sites. As patients are randomized to the two treatment groups, no additional adjustment for potential confounding variables is anticipated to be necessary. Subgroup analyses will be performed on patients undergoing a hysterectomy for pelvic pain and patients who undergo a laparoscopic hysterectomy without concomitant procedures. The final analysis will be conducted at the 0.05 level of significance and the interim analysis will be conducted at the 0.002 level of significance (to minimize type I error). Statistical analysis will be performed using appropriate statistical software and with the assistance of a biostatistician.

XXI. Data monitoring:

The principal investigator will review and investigate any study-related complications, if they occur. An analysis of the data will be performed as necessary pursuant to any complications observed, and at the study mid-point. The principal investigator will be in charge of deciding if the study should be stopped based on these analyses. There will be continuous monitoring of events by the principal investigator and prompt reporting of complications to the IRB, in accordance with the study's Data and Safety Monitoring Plan (DSMP). The principal investigator will also keep track of investigator deviations in terms of informed consent processes and the study protocol, and all repeat deviations will be reviewed.

Any unanticipated adverse events or risks to subjects will be reported to the Partners Human Research Committee (PHRC) in accordance with PHRC unanticipated problems reporting guidelines. Adverse events will be reported according to pre-established guidelines such that the relationship of the risks and benefits to subjects participating remains acceptable throughout the conduct of the study. Reports of unanticipated problems involving risks to subjects or others will be tracked on an adverse event tracking log and submitted through Insight/IRB within five working days/seven calendar days of the date the investigator first becomes aware of the problem. Adverse events and minor deviations tracking logs will also be maintained in-house.

XXII. Harms:

Great care will be taken to use the correct dose of each medication and avoid intravascular placement. Resuscitative equipment will be immediately available should an adverse event occur. Should an unforeseen adverse event arise that appears related in any way to the study, the principal investigator will halt the study and report the event to the IRB.

With regard to the risk of disclosure of confidential patient information, all possible precautions will be taken to ensure the confidentiality of study data. Any identifying information will be kept in password-protected computer systems or in locked file cabinets accessible only to the study staff.

XXIII. Auditing:

The data will be audited by the IRB at their discretion.

ETHICS AND DISSEMINATION

XXIV. Research ethics approval:

IRB approval will be obtained at participating sites.

XXV. Protocol amendments:

Protocol amendments will be communicated to the IRB and approval obtained prior to implementation.

XXVI. Consent or assent:

Informed consent will be obtained by participating surgeons on the day of surgery. Eligible subjects will be contacted prior to surgery and provided details of the trial, a copy of the consent form, and a decline card.

XXVII. Confidentiality:

Confidential patient information and any identifying information will be kept in password-protected computer systems or in locked file cabinets accessible only to the study staff.

XXVIII. Declaration of interests:

The investigators declare no conflicts of interest.

XXIX. Access to data:

Data access will be restricted to study investigators and research assistants.

XXX. Ancillary and post-trial care: None

XXXI. Dissemination policy:

Subjects will be informed of the treatment arm they were assigned to at their follow-up visit. Trial results will be publicly available upon publication of the study. Authorship eligibility will include those investigators involved in major portions of the study design, collection, management, analysis, interpretation of results, or writing of the report.

APPENDICES

XXXII. Informed consent materials: Appendix

XXXIII. Biological specimens: None

XXXIV. Images:

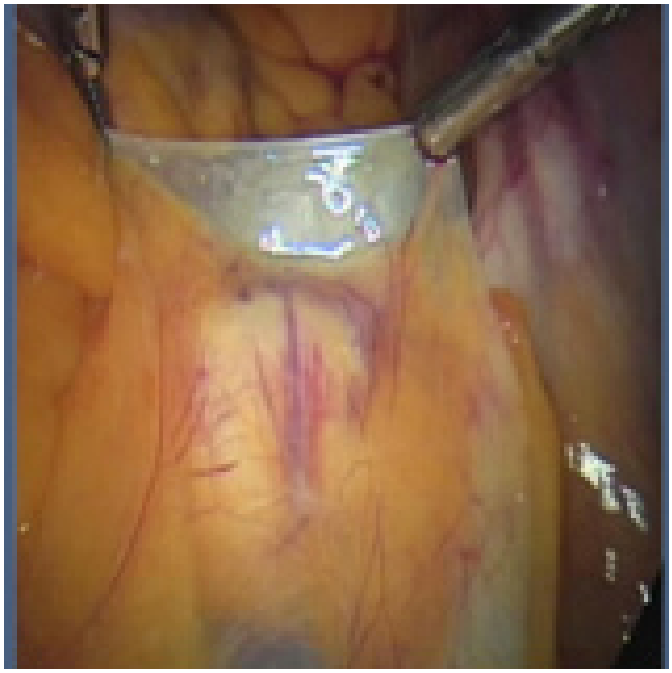

Figure 1. Laparoscopic view of the presacral space demonstrating tenting of the peritoneum prior to injection of the superior hypogastric block.

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Protocol devised according to the SPIRIT 2013 Guidelines (Chan A, Tezlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med. 2013;158:200-7.