Study Protocol:
Intraoperative local anesthesia for management of postoperative pain following laparoscopic ventral hernia repair: a prospective double-blind randomized trial
“Lap Hernia Study”

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Co-Investigators: Anthony Anagnostou MD, Farida Bounoua, MD, Kevin Cahill, MD, Steve Chang, MD, Zach Deboard, MD, Shawn Diamond, MD, Mark Donovan, MD, Jeffrey Gauvin, MD, Aimee Gough, MD, Jonathan Grotts, MA, Stephen Kaminski, MD, Maria Nelson, MD, Anthony Pozzessere, MD, Subhash Reddy, MD, Nicolas Saenz, MD, Mike Salehpour, MD, Rohit Sharma, MD, Lisa Small, MD, Christopher Taglia, MD, Erin Thompson, MD, Burgundy Tyrrel, MD, Amber Waits, MD, Nathaniel Wolkenfeld, MD, Samantha Yim, RN, BSN, Marc Zerey, MD

Background

Laparoscopic ventral hernia repair is a well-established treatment strategy for ventral hernias. Several studies have documented the advantages of laparoscopic repair compared to open ventral herniorrhaphy[1]. Intense pain immediately following laparoscopic ventral hernia repair is common, resulting in patients staying in the hospital for an average of 2 days for pain management[1]. Many methods for controlling this pain have been studied with varying success [2-4]. We are proposing to use a local analgesic injection between the abdominal wall and mesh intraoperatively. By placing the injection of the local analgesic in this location, the medication will spread throughout the area of operation where patients experience the most pain postoperatively. The local analgesic involved in the study is bupivacaine. This drug is indicated for infiltration, epidural, nerve blocking, and other types of anesthesia. We believe bupivacaine is the ideal drug for this study because it has a long duration, often lasting up to 20 hours. Our method for postoperative pain management is unique because we are addressing the pain intraoperatively with a drug known for its long duration.

Objectives

The primary objective of this study is to test different methods for pain management following laparoscopic ventral hernia repair. We hypothesize that local analgesic injection between the abdominal wall and mesh intraoperatively during laparoscopic ventral hernia repair will result in a 20% decrease in the use of post-surgery pain medication in the first four hours after surgery. Secondary endpoints include nausea/vomiting, time to diet intake, time to ambulation, pain medication used during entire postoperative hospital stay, and postoperative pain reduction.
Study Population

We will identify patients undergoing laparoscopic ventral hernia repair at Santa Barbara Cottage Hospital (SBCH) before the scheduled surgery from the Surgery Department’s operative log.

Inclusion Criteria:
1. Patient must be scheduled for a laparoscopic ventral hernia repair at SBCH. If any additional procedure is performed, the subject will be excluded from the study
2. Age 18 or older
3. Patient must agree to complete pain journal postoperatively
4. Informed consent signed and dated by patient. Consenting through a legally authorized guardian will not be accepted due to the necessity of completing a subjective pain journal

Exclusion Criteria:
1. Any surgical procedure occurring besides the study procedure
2. Any allergy or sensitivity to bupivacaine or its derivatives
3. Less than 18 years of age
4. Patient unable to self report in pain journal due to cognitive disabilities
5. Discharged less than 4 hours post-surgery

Study Methods and Procedures

This is a randomized double-blind, placebo-controlled study. We will identify patients undergoing laparoscopic ventral hernia repair at Santa Barbara Cottage Hospital (SBCH) before the scheduled surgery from the Surgery Department’s operative log.

During the patient’s preoperative visit before the day of surgery, a study team member will contact the potential subject, screen for enrollment criteria and present the informed consent form. The patient will be given time to consider participation in the study. On the morning of a potential study subject’s surgery, a member of the study team will confirm that the patient is undergoing surgery on that day. Patients will either sign the informed consent form during the preoperative visit before the day of surgery or the patient will be given the opportunity to finish the consenting process on the day of surgery in the Surgical Admitting Department.

Once a patient has consented to participate in the study, the medical record will be reviewed to capture such data as, type of hernia, medical and surgical history, and current medications. The subject may be interviewed if any of the previous information is not clearly stated in the chart. Additionally, we will ask the subject for a baseline pain score and review forms the subject will complete after surgery. A brightly colored enrollment information card will be placed on the patient’s chart to identify the subject’s participation in this study. This identification card will include information to staff treating the research subject. The study team will also contact the Pharmacy Department.
with a written order and a subject number immediately following the consenting process. The Pharmacy will refer to a randomization plan and provide a blinded vial to Operating Room (OR) staff for use on the subject. The vial will contain either a normal saline solution or bupivicaine but the label on the vial will say “bupivicaine 0.5% OR Normal Saline”. This process will maintain the blinding of the study drug to the study team. The Pharmacy will maintain the randomization plan and is responsible for breaking the blinding if the investigators decide it is medically necessary (e.g. occurrence of adverse reaction). Upon conclusion of the procedure, before desufflation, the study trained surgeon will inject study drug in the amount of 1 cc per 1 cm of greatest diameter mesh in the area between the mesh and the abdominal wall, coating the tacks with the study drug and layering the fluid on top of the mesh. There are minimal anticipated risks to the patients enrolled in this study but possible adverse reactions include, but are not limited to, an anaphylactic reaction to bupivicaine, shortness of breath, wheezing, hypotension, or hemodynamic instability. Occurrences of adverse reactions will be monitored by hospital nursing staff and any adverse reactions will be immediately reported to the primary surgeon for treatment. The primary surgeon is responsible for determining if an adverse reaction or other clinical circumstance necessitates unblinding of study drug to investigators. The OR staff will be trained in the study protocol and procedure, which includes using standard sterile technique to provide the blinded study solution to the surgeon for use on the research subject. The OR staff will also be responsible for documenting the date and time the solution was used.

Patients receiving the bupivicaine injection will be considered the treatment group and the control group will be patients receiving the injection of saline. An injection of bupivicaine or saline after hernia repair is the only difference between the care given to the control and treatment groups as a result of being enrolled in this study. Study subjects may receive unique treatment for medical conditions at the doctors’ discretion and we will attempt to control for this during data analysis. The investigators will cover the cost of bupivicaine for patients in the treatment group so that the patients will not be responsible for paying for any part of the research.

After a subject’s surgery is finished, we will follow the patient in the hospital for the course of his/her inpatient stay. Patients enrolled in this study are expected to leave the hospital at varying times, but a subject who does not stay for a minimum of four hours after surgery will be excluded. The Director of the CHS Department of Anesthesia and his staff are aware of this research project. They have agreed to limit postoperative pain medication to Demerol, Dilaudid, Fentanyl, and Morphine. We have asked them to limit their pain medication to these drugs because these specific drugs can be standardized for analysis. There is a possibility that anesthesiologists may not comply with our request and we may have to remove a patient from the study if he/she receives a drug that cannot be used for our analysis. Norco is generally the preferred pain medication given to patients once they are able to tolerate liquids. This medication is administered by the surgeon after they leave the care of the anesthesiologist and we will document Norco dosing for analysis. Once a patient leaves the Post-Anesthesia Care Unit he/she will be provided with forms to document pain (Appendix A). We will ask participants to rate pain while at rest, sitting, walking, and coughing every 30 minutes for the first one and a half hours after patients leave the Post-Anesthesia Care Unit, then every hour while
awake for the next 24 hours, and finally every 4 hours until hospital discharge using a numerical rating scale (NRS). A NRS is a self-administered single-item pain questionnaire which asks patients to rate pain from 0 (no pain) to 10 (worst imaginable pain). This collection of patient-reported NRS is referred to as a pain journal. Included with the pain journal are questions about time to regular diet intake and occurrences or frequency of nausea/vomiting. A review of patients’ charts will be conducted once patients are discharged from the hospital. Data we will gather from patient charts includes medications, number of tacks used during surgery, size of mesh used during surgery, size of hernia, and time/date of investigational procedure (Appendix B).

The principal investigator Dr. David Thoman will be responsible for the design, maintenance, and consenting process of the study in consultation with his co-investigators and study coordinators. The Department of Anesthesia is responsible for using a pain management plan that complies with the study protocol. Ancillary Surgical Services staff will be responsible for assisting with the delivery of normal saline or bupivicaine to the surgeon and documenting time and date of delivery to patients. Pharmacy will be responsible for maintaining the randomization plan. Post-Anesthesia Care Unit nurses and Floor staff will administer the pain control survey. Dr. David Thoman will serve as a study mentor for Dr. Reddy, as well as referring his potential patient population, and Jonathan Grotts will assist with statistical analysis and research design. The Research Coordinators from the Department of Research at SBCH will share the responsibility, along with other members of the study team, of consenting patients, distributing the pain journals, abstracting data from charts, and maintaining the operational needs of the project.

**Risks and Benefits**

There are a number of risks associated with surgical hernia repair, but this study adds minimal additional risks to the surgical procedure. We will screen patients for any allergies to bupivicaine and its derivatives during the consenting process because there is a risk associated with allergic reactions to this drug. Any patient with a known allergy to bupivicaine or its derivatives will be excluded from the study. Possible adverse reactions patients might experience while enrolled in this study include, but are not limited to, an anaphylactic reaction to bupivicaine, shortness of breath, wheezing, hypotension, or hemodynamic instability. Occurrences of adverse reactions will be monitored by hospital nursing staff and any adverse reactions will be immediately reported to the primary surgeon for treatment. Enrollment in this study is voluntary and patients may withdraw at any time, including if they feel that the postoperative surveys are too cumbersome.

There are no known benefits to subjects that enroll in the study. There are potential benefits to future patients undergoing a laparoscopic ventral hernia repair if we can show that the administration of bupivicaine after hernia repair results in the use of less postoperative pain medications and less self-reported pain during postoperative hospital stay.
Clinical Data Management

Study coordinators will be responsible for the management of data including pain journals and post-discharge chart review. The Pharmacy Department will maintain the randomization plan. Data will be stored in a locked cabinet and then entered into a password protected spreadsheet. We will store data for six years after the study is closed. A list of the data we are interested in collecting is presented in the Appendices.

Statistical Methods and Planned Analysis

The primary endpoint is aggregate pain medication use in the four hour window after surgery. We will compare the treatment and control groups for this endpoint using a multiple regression model. There are a variety of different pain medications used postoperatively and we will standardize doses through validated conversion equations[5]. We stipulate that the pain medications used will be Demerol, Dilaudid, Fentanyl, and Morphine and we will convert all pain medication to milligrams of Morphine for comparison. Demographics and initial medical conditions of the treatment and control groups will be compared for consistency using t-tests, Wilcoxon Rank Sum Tests, and Chi-Square Tests. Time to regular diet intake, time to ambulation, and frequency of nausea/vomiting will be compared using a linear regression model. Numerical Rating Scales from the patients’ pain journals will be compared by averaging measurements in the first hour and a half after patients leave the Post-Anesthesia Care Unit and then averaging every four hours for the first 24 hours awake and then averaging every eight hours till discharge to reduce the influence of measurements taken immediately following administration of narcotics. A longitudinal regression model will be used to analyze patient-reported pain over time. Survival analysis will be used to analyze time to discharge.

We submitted a preparatory to research application through the Cottage Health System Institutional Review Board and received data on the amount of narcotics used after laparoscopic ventral hernia repair in three patients who did not receive a bupivacaine injection to the abdominal wall intraoperatively. Using this data, we computed that the average milligrams of Morphine administered in the first four hours after surgery was 7.27 (+/- 1.17 SD). Sample size calculations were computed using these baseline numbers with statistical software and we found that we will need to gather data on 80 patients (40 patients in the treatment group and 40 patients in the control group) to show a decrease of 20% in pain medication use in the first four hours after surgery with a power of 0.95.

Literature References


Appendices

Appendix A- Pain Journal
Appendix B- Data Collect Forms
Appendix A

Intraoperative local anesthesia for management of post-operative pain following laparoscopic ventral hernia repairs: a prospective double blinded randomized trial.

IRB# 11-20

Thank you for participating in the above trial.

Pain Journal.

Your completion of the following information is vital to the study’s success. Please follow the instructions below.

Instructions:
1. Complete the pain journal entries as noted in the following pages.
2. Use the numerical rating scale (NRS) to select an answer.

3. Answer any other questions you see on the following pages.
4. At Discharge: Please give your completed pain journal to your nurse.
5. Staff Nurse: Please call Research for pick up of Pain Journal 569-7461.

Any questions: 569-7461
<table>
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<tr>
<th>Date</th>
<th>Time</th>
<th>Pain Level</th>
<th>Sits or STA</th>
<th>Walking</th>
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**Every 30 min. x 3**

1) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

2) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

3) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

**Then every 1Hr while awake**

1) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

2) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

3) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

4) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

5) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

6) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

7) Date ____________
   Time ____________
   Pain Level: Yes
   Sits or STA: Yes

- Every 30 min. x 3
- Every 1 hr x 24 hrs (while awake)
- Every 4 hrs until discharge home

1) Date/Time of first walk:

2) Date/Time you tolerated a regular diet (solid foods):
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<th>Time</th>
<th>Resting</th>
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### Appendix B

#### Every 1 hour while awake

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#### Then every 4 hours while awake

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**THANK YOU!**
**Pre Operative Data Collection**

**Age:**
**Gender:**
**Allergies:**

**Medical/Surgical Hx:** (including pain hx if applicable)

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<th>Diagnosis</th>
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**Current Medications:**

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**Type of Hernia**

(Circle one)
- Incision
- Spontaneous
- Traumatic

**Baseline Pain Level (0-10) and Location:**

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<th>Pain Level Now:</th>
<th>Location:</th>
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‘**Surgery Study Documentation**’

This patient is enrolled in the Laparoscopic Ventral Hernia Repair Study

Pt Sticker
**Please complete the following information and place in front pocket of the chart for study coordinator. **

1. Patient study medication documentation (bupivicaine vs. placebo):

<table>
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<tr>
<th>Date</th>
<th>Time</th>
<th>Volume used</th>
<th>Surgeon</th>
<th>Signature</th>
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(1 cc per 1 cm of greatest diameter mesh in the area between the mesh and the abdominal wall, coating the tacks with the study drug and layering the fluid on top of the mesh.)

2. Number of tacks used: _______

3. Absorbable tacks? Yes/ NO (circle one)
   Type of Tack (Brand/Size): _______________________________

4. Number of hernias: _______ - covered by 1 mesh? Yes/No (if >1 mesh, pt excluded)

5. Total hernia size: _______ cm X _______ cm (add length and widths if >1)

6. Size of the mesh: _______ cm X _______ cm
   OR _______ cm circular

7. Was there a primary closure? YES / NO (circle one)

8. Transfacial Sutures: YES / NO

For any questions: Research ext: 5-7461, Samantha @ 729-4862, or Dr. Gough @ 455-2023