Effects of Local Anesthesia on Post-operative Pain During Laparoscopic Inguinal Hernia Repair

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Protocol:

A randomized, double-blinded, placebo-controlled trial of the effects of instilling local analgesia on post-operative pain during laparoscopic inguinal hernia repair.

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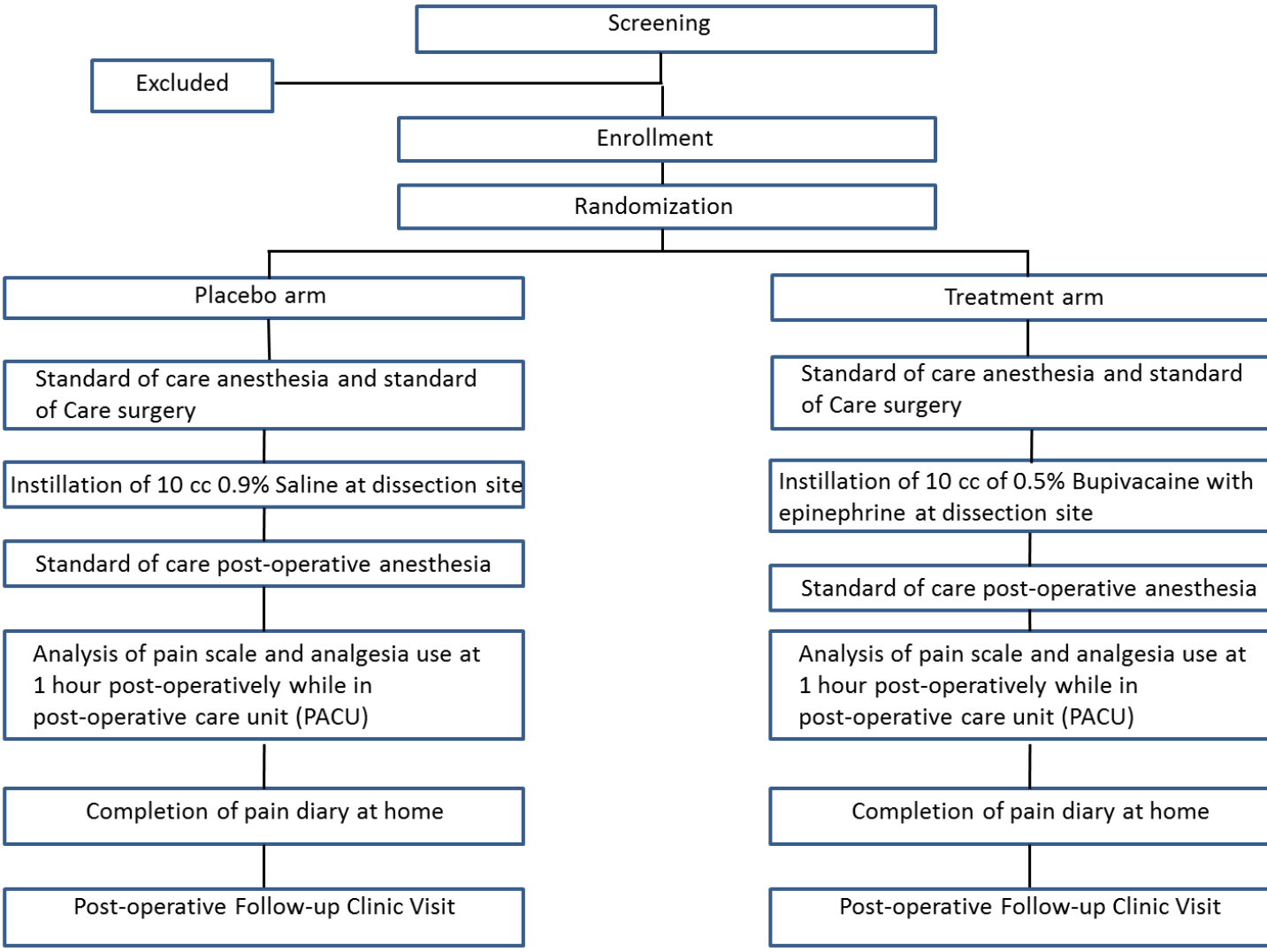
Study Schematic



Background:

Controlling post-operative pain is a standard part of managing any post-operative patient. Laparoscopic Total Extraperitoneal (TEP) Herniorrhaphy is a widely accepted technique to repair inguinal hernias and is offered to patients in our practice.[1] The surgery requires general anesthesia and patients typically experience a significant amount of pain during the first post-operative day, at the incision sites, but more-so in the abdominal wall.[2] Local anesthetics such as Lidocaine and Bupivicaine are commonly used for regional anesthesia in most surgical settings. These agents block the voltage-gated sodium channels of neuronal membranes halting the rate of depolarization or conduction of pain response from pain receptors to the brain. They are widely used, very safe and highly effective. The use of these agents have been described to prevent post-operative pain in laparoscopic surgery for

[1] McKernan JB, Laws HL. Laparoscopic repair of inguinal hernias using a total extraperitoneal prosthetic approach. *Surg Endosc.* 1993;7:26-28.
[2] Edelman DS, Misiakos EP, Moses K. Extraperitoneal laparoscopic hernia repair with local anesthesia. *Surg Endosc.* 2001; 15:976-980.

cholecystectomy, appendectomy and gynecologic surgery.[3,4,5] The TEP technique, in contrast to intra-abdominal surgeries, remains entirely in the anterior abdominal wall where a temporary space between the muscle and connective tissue is made to repair the defect and place a piece of mesh. This site of surgical dissection and trauma is a potential target for use of local anesthetics to decrease post-operative pain. There have also been a small number of studies describing the use in laparoscopic hernia repair with contrasting conclusions, three reporting significant reductions in post-operative pain with the use of intraperitoneal anesthetic and four studies suggesting no difference.[6,7,8,9,10,11,12] In addition, these reports are limited by small enrollment sizes in a wide variety of sample populations internationally, (only one conducted in the United States in 1998), using a broad range of analgesia and anesthetic practices. Thus, the utility of local anesthetic in this setting remains at the forefront of debate. Clearly, a prospective, randomized, placebo-controlled study with a larger sample size in a more representative population is needed to draw practice-changing conclusions.

Objectives:

Primary Objective: To assess effect of local anesthetic into the preperitoneal space during laparoscopic hernia repair on post-operative pain.

Methods:

Patients with the clinical diagnosis of inguinal hernia, consented for elective laparoscopic inguinal hernia repair with mesh at Lahey Clinic Burlington by one of the General Surgeons listed in this study, will be randomized to two groups: the placebo group and the treatment group. The surgeons and the patients will be blinded to the allocation into the treatment and placebo arms of the study. The surgical approach to all patients will be the standard approach for laparoscopic inguinal hernia repair with general anesthesia. This standard will include both groups receiving 5 cc of 0.5% bupivacaine with epinephrine instilled at the umbilical port site and 2.5 cc instilled at

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[3] Alkhamesi NA, Peck DH, Lomax D, Darzi AW. Intraperitoneal aerosolization of bupivicaine reduces postoperative pain in laparoscopic surgery: a randomized prospective controlled double-blinded clinical trial. *Surg Endosc.* 2007;21:602-606.

[4] Thanapal MR, Tata AJ, Subramaniam T, Tong JMG, Palayan K, Rampal S, Gurunathan R. Pre-emptive intraperitoneal local anaesthesia: an effective method in immediate post-operative pain management and metabolic stress response in laparoscopic appendectomy, a randomized, double blinded, placebo-controlled study. *ANZ J Surg.* 2012, Oct 11.

[5] Sripada S, Roy S, Mathur M, Hamilton M, Cranfield K, Bhattacharya S. A prospective double-blinded randomized controlled trial of intraoperative pelvic instillation with bupivicaine for management of pain following laparoscopy and dye. *Br J Obstet Gynaecol.* 2006; 101:835-838.

[6] Deans GT, Wilson MS, Brough WA. Controlled trial of preperitoneal local anesthetic for reducing pain following laparoscopic hernia repair. *British J Surg.* 1998;85:1013-1014.

[7] O'Riordain DS, Kelly P, Horgan PG, Keane FBV, Tanner WA. A Randomized Controlled Trial of Extraperitoneal Bupivacaine Analgesia in Laparoscopic Hernia Repair. *Amer J Surg.* 1998; 176:254-257.

[8] Saff GN, Marks RA, Kuroda M, Rozan JP, Hertz R. Analgesic Effect of Bupivicaine on Extraperitoneal Laparoscopic Hernia Repair. *Anesth Analg.* 1998;87:377-81.

[9] Bar-Dayan A, Natour M, Bar-Zakai, Zmora O, Shabtai M, Ayalon A, Kuriansky J. Preperitoneal bupivicaine attenuates pain following laparoscopic inguinal hernia repair. *Surg Endosc.* 2004;18:1079-1081.

[10] Hon SF, Poon CM, Leong HT, Tang YC. Pre-emptive infiltration of Bupivicaine in laparoscopic total extraperitoneal hernioplasty: a randomized controlled trial. *Hernia.* 2009;13:53-56.

[11] Suvikapakornkul R, Valaivarangkul P, Noiwan P, Phansukphon T. A Randomized Controlled Trial of Preperitoneal Bupivicaine Instillation for Reducing Pain Following Laparoscopic Inguinal Herniorrhaphy. *Surgical Innov.* 2009;16:117-123.

[12] Abbas MH, Hamade A, Choudhry MN, Hamza N, Nadeem R, Ammori BJ. Infiltration of wounds and extraperitoneal space with local anesthetic in patients undergoing laparoscopic totally extraperitoneal repair of unilateral inguinal hernias: A randomized double-blinded placebo-controlled trial. *Scand J Surg.* 2010;99:18-23.

each of the 5mm port sites prior to incision. After deployment of mesh in the preperitoneal space of the abdominal wall during the procedure, the placebo group will receive the infusion of the 10cc 0.9% Saline in this space, and the treatment group will receive instillation of 10cc 0.5% bupivacaine with epinephrine. Post-operatively, the patient will receive the standard of care analgesia and post-operative care. The patient will be asked to rate pain using the Visual Analog Scale (VAS) hourly post-operatively until discharge. The nurse assigned to the patient's care in the Post-Anesthesia Care Unit (PACU) will administer the VAS score – they already do this as part of their practice – they will do it for every hour that the patient is in recovery room. The patient will be given a pain diary that they have been educated on during the pre-operative evaluation describing their pain and their management at home, to be returned at their post-operative follow-up visit in clinic within 4 weeks. . Pain will be self-assessed using the same VAS pain scale used in the immediate post-operative pain assessment. Analgesia dosages will be recorded post-operatively, and duration of analgesia taken at home will be recorded.

Recruitment:

The patients will be recruited and consented for the study in the clinics of the above listed General Surgeons. We calculated the sample size required so we have a power of 90% with intention to treat of detecting at least a 27% reduction of pain score with a 2-tailed test at $P \leq .05$. This number came to 114. We added 10% to account for possible loss of subjects to achieve an enrollment target of 125.

Inclusion Criteria:

- Age $\geq$ 18 with unilateral or bilateral inguinal hernia for laparoscopic repair
- American Society of Anesthesiology (ASA) Class I and II

Exclusion Criteria:

- Conversion from laparoscopic to open surgery
- History of chronic pain or ongoing treatment for chronic pain
- Age <18
- Allergy to local anesthetics

Human Protection Plan:

Informed Consent:

Informed consent will be obtained using attached form following the Standard Operating Procedures for Informed Consent (see attached form SOP#: IC607-S). Consent will be obtained by the principle investigator, co-investigators or the research coordinator. Those subjects unable to read or sign will be consented with a witness and those unable to speak English will be consented with a translator, following Standard Operative Procedures (see attached forms SOP#: IC608-S and SOP#: IC605-S)

Adverse effects and unanticipated problems:

Adverse reactions are rare and dose-dependent. Serious reactions are extremely infrequent and preventable with proper dosage calculations. [13],[14] Maximum Dose: 90mg for adult. 0.5% Bupivicaine 5mg/mL with epinephrine. (15 mL, a total of 75mg will be given) .

- Adverse effects of Local Anesthetic:
- Common: (= to 10% or more) None
- Less Common: (= to 3-9%) None
- Rare (=2% or less) None
- Very Rare: (=1% or less)
  - Local reactions (1.9/10,000) : local parasthesias (sensation of tingling, tickling, burning or numbness)
  - Systemic Toxicity (7.5/10,000)
    - CNS toxicity: perioral/tongue parasthesias, tremors, dizziness, slurred speech, double vision, tinnitus (ringing in the ears), confusion, restlessness, convulsions, seizure
    - Methemoglobinemia
    - Cardiovascular toxicity: bradycardia (slow heart rate), arrhythmias (abnormal rhythm)
    - Allergic reaction: skin redness and swelling, itchy rash, shortness of breath, throat swelling, low blood pressure

All internal adverse effects will be reported to the IRB using the Unancticipated Problem Report (see attached). If serious, this will be reported to the expedited IRB within 10 working days/14 calendar days. If non-serious this will be reported to the full IRB within 20 working days/30 calendar days.

Benefit:
Local anesthetics are safe and effective agents widely-used in surgical specialties to induce absence of pain sensation. 0.5% is a standard dose of Bupivicaine used in surgery and will be used in this study. The anesthetic will be instilled through a laparoscopic port trocar into the preperitoneal space, the site of the majority of surgical dissection and location of mesh placement. The risks are almost negligent for local anesthetic as described and maximum doses of 175mg will not be exceeded. The potential benefit is improved post-operative pain, less post-operative stress maximizing patient comfort and recovery while minimizing additional IV and oral analgesics necessary post-operatively.

Subject Reimbursement:

None

Data Analysis:

We calculated the sample size required so we have a power of 90% of detecting at least a 27% reduction of pain score with a 2-tailed test at $P \leq .05$. This was done using the data in our literature review, which described a mean post-operative VAS pain score in the placebo group of 3.57 with a standard deviation of 1.47, and a mean difference between groups of 1.23, calculating the effect size at 0.84 (1.23/1.47). At 90% power and an effect size of 0.84, a total of 64 total patients is needed for significant conclusions in a parallel study, 32 in each arm. We added 10% to the total sample size for intended enrollment to account for potential lost subjects during the trial.

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[13] Cox B, Durieux ME, Marcus MA. Toxicity of local anesthetics. *Best Pract Res Clin Anaesthesiol*. 2003 Mar;17(17(1):111-36

[14] Moore PA, Hersh EV. Local Anesthetics: Pharmacology and Toxicity. *Dent Clin N Am.* (2010) 587-599

Our statistician will provide randomization to the inpatient pharmacy who will provide the OR with the blinded study solution. Statistical data will be based on an intention-to-treat principle. Data collection will be managed by the Research Coordinator and entered in an identifier-free, password-protected database. The Mann-Whitney U test will be applied to data on pain score and analgesia required while Fisher's exact test will be used to calculate association of secondary outcomes.

Appendix:

- Informed Consent Form
- Standard Operating Procedures Informed Consent
- Standard Operating Procedures Informed Consent Unable to sign/speak
- Standard Operating Procedures Informed Consent Non-English Speaking
- Unanticipated Problem Report Form