PROSPECTIVE RANDOMIZED CONTROLLED STUDY OF AN ENHANCED RECOVERY PROTOCOL FOR ANORECTAL SURGERY

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Protocol No./ Title:	Prospective Randomized Controlled Study of an Enhanced Recovery Protocol for Anorectal Surgery
Study Rationale:	Anorectal surgery is primarily performed in an ambulatory setting (>90%) and has been shown to be safe and effective.[1] Postoperative pain control remains one of the largest impediments to excellent postoperative recovery. Mostly, pain is treated with opioids and these are historically considered "safe" drugs as they do not impose an increased risk of bleeding, kidney, or stomach problems. However, many patients taking high dose opioids have a higher risk of constipation. In addition, rising concern over the opioid epidemic has piqued patients and provider interest in reduction of opioid use in the postoperative setting[2] Few studies exist regarding enhanced recovery after surgery (ERAS) in anorectal surgery. Parrish et al. looked at an ERAS protocol for ambulatory anorectal surgery after a broad range of procedures in a retrospective analysis across multiple hospitals and found that given a 7 step ERAS protocol, patients had decreased postoperative pain and decreased returns to emergency care. However, there was low overall adherence to the protocol, significant variability across each patient's care, and they did not look at postoperative pain after the patient left the hospital.[3] Toyonaga et al. showed that decreasing intravenous fluids (IVF) intraoperatively, preoperative analgesia, and well-controlled postoperative pain can decrease postoperative urinary retention after anorectal surgery[4] Van Backer's small randomized controlled trial (RCT) looked at preoperative analgesics and their effect on postoperative pain and found that there was significantly less pain, and narcotic requirement in the immediate postoperative period.[5] To date, no prospective studies exists evaluating postoperative pain and narcotic utilization in the postoperative period with multimodal ERAS pathway versus standard of care after anorectal surgery. We hypothesize that ERAS with a multimodal preoperative and postoperative pain management pathway can reduce narcotic utilization and pain during the first postoperative week after anorectal surgery. In this randomized clinical trial, we will compare postoperative narcotic utilization, pain, complications, hospital readmission, and overall patient satisfaction after anorectal surgery.
Study Population:	80 patients undergoing either hemorrhoid or anal fistula surgery (up to 88 will be recruited as needed to account for any withdrawals).

Hypothesis:	Multimodal ERAS pathway will result in decreased requirement of oral morphine equivalents in the 1-week postop period (Arm 1) vs. anorectal surgery without ERAS pathway (Arm 2) Our secondary hypotheses are: The ERAS group will have decreased mean pain score and pain on defecation at 1 week postoperatively. There will be no significant difference in adverse events and analgesic related adverse events between the two groups.
Study Design:	Single center prospective randomized controlled trial performed in patients undergoing elective hemorrhoid or anal fistula surgery. There will be 2 arms: Arm 1 will receive multimodal ERAS and Arm 2 anorectal surgery without ERAS Arm1 (Multimodal ERAS): 1) In preoperative care unit patients will be administered with a sip of water oral gabapentin 600mg and oral acetaminophen 1,000mg 2) Patients will be asked to void to empty their bladder in the 30 minutes prior to surgery 3) Monitored anesthesia care will be the preferred anesthesia choice however, cases thought to benefit from general anesthesia will be allowed. 4) Fluids will be minimized to < 500 ml during the operation and postoperative period 5) Intraoperative: IV ketorolac 30mg will be administered by anesthesia 6) Fentanyl IV will be administered in incremental doses of 25 mcg during surgery based on anesthesiologist best judgment of pain response 7) Perianal and bilateral pudendal nerve block using 30 ml total volume of 0.25% bupivacaine with epinephrine 1:200,000 and dexamethasone 8 mg 8) Postoperative pain control: a. Gabapentin oral 300 mg qHS (#42, refill #1) b. Acetaminophen oral 1000mg TID (#42, refill #1) c. Ketorolac oral 10 mg TID (#15, refill #0) d. Oxycodone oral 5 mg PRN every 6 hours (#30, refill #0) 9) Postoperative laxative regimen: a. Daily MiraLAX® 1 scoop in 1 glass of water for 15 days b. Daily milk of magnesia 1 tablespoon if no bowel movement by POD2 until regular bowel movements c. Daily mineral oil 1 table spoon if no bowel movement by POD2 until regular bowel movements

	Arm 2 (Anal surgery without multimodal ERAS pathway): No preoperative pain medications will be administered 1) Monitored anesthesia care will be the preferred anesthesia choice however, cases thought to benefit from general anesthesia will be allowed. 2) Patients will be asked to void to empty their bladder in the 30 minutes prior to surgery 3) Fluids will be minimized to < 500 ml during the operation and postoperative period 4) Fentanyl IV will be administered in incremental doses of 25 mcg during surgery based on anesthesiologist best judgment of pain response 5) Perianal and bilateral pudendal nerve block using 30 cc total volume of 0.25% bupivacaine with epinephrine 1:200,000 6) Postoperative pain control: a. Oxycodone oral 5 mg PRN every 6 hours (#30, refill #0) b. Patients will be allowed to take oral acetaminophen and ibuprofen over the counter if needed but active narcotic-sparing pain management regimen will not be implemented 7) Postoperative laxative regimen: c. Daily MiraLAX® 1 scoop in 1 glass of water for 15 days d. Daily milk of magnesia 1 tablespoon if no bowel movement by POD2 until regular bowel movements Daily mineral oil 1 table spoon if no bowel movement by POD 2 until regular bowel movements
Randomization:	Randomization will be performed via online randomization program: sealedenvelope.com 80 patients will be randomized in blocks of 4 and stratified by treatment (hemorrhoid or fistula surgery). NOTE: Up to 88 subjects may be recruited in order to account for any withdrawn subjects).
Primary Endpoint:	Total narcotic use in the 1-week period postoperatively in oral morphine equivalents
Secondary Endpoints:	1. Total narcotic use in the 1-week period postoperatively in oral morphine equivalents 2. Postoperative pain score on arrival to postoperative care unit (PACU) and upon discharge from PACU 3. Postoperative nausea 4. Maximum daily pain score recorded by patient daily log (mean of days 1-7) 5. Maximum daily pain score recorded by patient log (mean of days 8-14)

	6. Mean pain on defecation score (days 1-7 and days 8-14) 7. Urinary retention and urinary function as measured by the international prostate symptom score 8. Presence of adverse events requiring return to emergency care (urinary retention, pain, nausea, constipation, infection, bleeding) 9. Adverse events possibly related to medication use assessed at 1 and 2-week postoperative visits (nausea, vomiting, dizziness, drowsiness, light headedness, amnesia, tremor, shortness of breath, chest pain, or any other adverse event reported by patient) 10. Time to first bowel movement
Data collection and measurement of endpoints	Patient demographics and preoperative characteristics will be collected from the patient medical record 1) Patient identifiers: medical record number, date of birth 2) Patient demographics; age at the time of surgery, gender, height and weight, race, ethnicity 3) Prior anorectal surgical history 4) Prior history of constipation and average standard interval between unassisted (if no laxative used) bowel movements 5) Presence of comorbid disease 6) Prior narcotic utilization and duration since last use 7) American Society of Anesthesiologist (ASA) classification Preoperative baseline pain will be measured in the preoperative care unit using VAS pain scale (0-10; 10 being worst imaginable pain) Preoperative baseline nausea will be measured in the preoperative care unit using a scale 0-2, 0 (no nausea), 1 (Nausea without vomiting), 2 (active vomiting) Preoperative urinary function will be assessed using validated instrument (International Prostate Symptom Score (I-PSS) Surgical characteristics 1) Type of surgery performed 2) Size of wound 3) Estimated blood loss 4) Type of anesthesia 5) Total narcotic dose in morphine equivalents administered in the OR 6) Volume of intravenous fluids administered Postoperative outcomes (PACU) 1) Pain (VAS) score on arrival and discharge from PACU 2) Nausea score (0-2) on arrival and discharge from PACU

	3) Volume of PACU intravenous fluids administered 4) Narcotic dose (morphine equivalents) administered in PACU 5) Ability to void prior to discharge home 6) Any patient reported adverse events Postoperative outcomes 1) Total narcotic utilization in the 1-week postoperative period will be calculated in oral morphine equivalents by asking the patient to bring in their pills for measurement of total used at their 1-week postoperative visits 2) Compliance with additional pain medications used will be performed in a similar fashion at 1 week 3) Compliance with laxative regimen will be assessed at 1-week postoperative visits 4) Patients assigned to standard of care will be asked if they used any additional over the counter medications 5) Any new prescriptions prescribed in the 1-week postoperative period will be recorded 6) Any refills on prescription medications will be recorded 7) Patient reported pain and nausea at the first 1-week postop period will be collected by asking the patient to fill out a pain and nausea daily log for the first 1-week postoperative period and bring the log to their 1 week and 1-week postop visits 8) A pain at defecation questionnaire will also be collected for 1 week after surgery and patients will be asked to bring this to their postop visit at 1 week. 9) The patient will be asked to log the day of their first postoperative bowel movement 10) A study investigator will assess the patient's postoperative urinary function (I-PSS) modified to include the previous 24 hours and previous week on POD 1 and 7 respectively 11) At 1-month postoperative visit, any additional adverse events or complications, urgent care, emergency department visits or hospital admissions will be collected
Subgroup Analysis:	Subgroup analysis will be performed for the following patient groups: 1. Patients undergoing hemorrhoid surgery 2. Patients undergoing anal fistula surgery
Safety Endpoints:	Number of adverse events related to gabapentin, acetaminophen, dexamethasone

Sample size:	With a sample size of 17 patients per arm for a total of 34 patients, this study will have 80% power to detect a statistically significant difference between the standard of care and multimodal ERAS assuming a mean oral morphine equivalent requirement of 60mg (SD 30mg) in the first postoperative week for the standard of care group, a 50% reduction total oral morphine equivalent requirement for the ERAS group to 30mg, with alpha less than 0.05. Due to lack of normality we will increase each group to 20 patients. In order to have enough power to analyze hemorrhoid surgery and anal fistula surgery patients separately in our subgroup analysis, we plan to include 80 patients total in our analysis with stratified randomization based on type of surgery. To allow for dropouts, 4 additional patients will be recruited per arm for a total of 88 patients.
Interim analysis:	An interim safety analysis will be performed at 50% subject accrual.
Key Inclusion Criteria:	1. Able to freely give written informed consent to participate in the study and have signed the Informed Consent Form; 2. Males or females, age 18 to 70 years old at the time of study screening; 3. American Society of Anesthesiologists (ASA) Class I-III (Appendix III) undergoing elective anorectal surgery 4. Patients undergoing the following hemorrhoid surgeries will be included: a. Excisional single column or multiple column hemorrhoidectomy including internal and external component b. Stapled hemorrhoidpexy (aka procedure for prolapsed hemorrhoids with or without excision of external hemorrhoid or skin tag) c. Trans anal hemorrhoidal dearterialization with mucopexy (THD) with or without excision of external hemorrhoid or skin tag 5. Patients undergoing the following anal fistula surgery will be included: a. Anal fistulotomy or fistulectomy of intersphincteric or transphincteric fistula with wound > 1 cm b. Endorectal or anocutaneous advancement flap for anal fistula repair c. Ligation of intersphincteric fistula tract (LIFT)

Key Exclusion Criteria:	1. Unable or unwilling to provide informed consent or comply with study procedures 2. American Society of Anesthesiologists (ASA) Class IV or V; emergency surgeries 3. Children <18 4. Patients over age 70 due to small risk of altered mental status with gabapentin in elderly[6] *5.* Patients with impaired renal clearance (baseline creatinine 1.5mg/dL, creatinine clearance < 60ml/min or known renal dysfunction) 6. Patients with known liver dysfunction (Childs class A, B, or C) 7. Patients with prior liver or kidney transplant 8. Pregnant patients 9.Patients requiring emergency surgery 10. Patients taking narcotics or steroids at the time of surgery 11. Patients having external hemorrhoidectomy or skin anal tag excision only 12. Patients having anal abscess drainage, seton placement without definitive fistula repair, subcutaneous fistulotomy or fistulotomy with wound <1 cm
Treatment Duration and procedures:	• **Screening**: Patients will be screened and enrolled in the study after review of their, demographics, medical history and physical exam. • **Day of Surgery**: Patients will be randomized to either of the 2 study arms: Arm1 (Anal Surgery with multimodal ERAS), or Arm2 (Anal surgery without multimodal ERAS pathway). • **Follow-Up Clinic Visit (7 days)** from surgery will be scheduled per standard of care. • **Follow-Up Clinic Visit (30 days)** from surgery will be scheduled per standard of care. Patients will be followed during the 1-month postoperative period. At their preoperative, 1 week, 2 week, and 30-day postoperative visits they will answer a subjective questionnaire. The preoperative questionnaire (Appendix B) will include any pain meds they currently use, average bowel movements per week, any baseline anorectal pain, presence of nausea, and IPSS, The postoperative PACU questionnaire (Appendix C) will include Pain (VAS) score post-surgery to discharge from PACU. Nausea score (0-2) post-surgery to discharge from PACU. Volume of PACU intravenous fluids administered. Narcotic dose (morphine equivalents) administered in PACU. Ability to void prior to discharge home, and any patient reported adverse events. The postoperative questionnaire (Appendix D) will include questions regarding medication taken for pain, nausea, and any meds not directly given postoperatively for pain. Adverse effects of any of the medications taken will be record-

	ed. Any prolonged urinary retention requiring return to emergency care. Constipation requiring a secondary agent (laxative other than the first line). Overall satisfaction with their care (0-10). They will then be followed up for 30-days after surgery and any complications occurring during that study period will be recorded. Any visits to the outpatient service, urgent care, or emergency department of issues relating to the surgery or medications, Any admissions to the hospital for related issues Patient participation in this study will end after 1 month.
Treatment Failure/ Discontinuation Criteria:	Patients will be discontinued from the trial at any time as a result of any other event (e.g., treatment-emergent serious adverse event, surgery) that in the opinion of the investigator warrants discontinuation from the trial. These include: • Drug allergy • Evidence of AKI, Bleeding, or other adverse events from the drugs. These events would be recorded but the patient would not be included in the postop pain analysis. • Patients with significant postoperative pain in the control group that is not adequately controlled with opioids and require additional pain medications. This would be recorded but the patient would be disqualified from the analysis • Any patient requiring an additional procedure during the study period

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