EFFICACY OF EXPAREL® ON POST-OPERATIVE PAIN AFTER RYGB USING EEA CIRCULAR STAPLER TECHNIQUE

Summary

This will be a head to head study that includes two cohorts of patients undergoing roux-en-y gastric bypass with the use of circular end to end anastomotic (EEA) stapler to create the gastro-jejunal anastomosis. One cohort (50 patients) will receive Exparel® (liposomal bupivacaine injection solution) injections intra-operatively at time of incision closure. The control cohort (50 patients) will receive standard bupivacaine injections at the time of incision closure, the current standard of care. Post-operative analgesia will be standardized and identical for both cohorts. The primary outcome will be pain scores and 24 and 48 hours post operatively, measure using the visual analog scale (VAS). Secondary outcomes will include the parameters included in the American Pain Society Post-Operative Questionnaire (APS-POQ-R), a validated measurement tool to assess how patients experience pain and how it may impact their ability to complete daily activity. Readmission, ED visits, and phone calls to clinic related to pain control will be evaluated by retrospective chart review at day 30 postop. This information may better direct surgeons in selecting type of injected medication at the incision site, in an effort to achieve better short-term results.

Background

Compared to open operation, laparoscopic surgery offers numerous benefits, including decreasing surgical trauma, improved cosmesis and decreased wound infection and wound related complications. Another significant advantage is the reduction of post-operative pain; however, effective post-operative analgesia following laparoscopy still often requires intravenous or oral narcotics. Several factors may contribute to the development of pain post-laparoscopic surgery, including the stretching of the intra-abdominal cavity, peritoneal inflammation and neuro-vascular irritation [1–3]. Lower intensity and duration of pain associated with laparoscopic surgery has been well documented when compared to laparotomy. Nevertheless safe peri-operative analgesic regimen that effectively achieves pain relief with minimal side effects is required, and it likely best achieved by a multimodality approach Reduction of pain may be achieved by early administration of analgesics, typically prior to patient awakening from anesthesia [1, 4–7]. Preventive analgesia includes any intraoperative analgesic agents/techniques that provides the ability to control pain-induced sensitization of the central nervous system and decrease the development of ongoing pain [1, 8, 9].

Commonly used non-opioid based medications such as acetaminophen (paracetamol) have been shown to reduce pain after various surgical procedures [1, 10, 11]. Local analgesia has also been shown to be effective adjunct in relieving pain related to laparoscopic surgery. [1, 9, 12, 13]. Bupivacaine is an amide-based local anesthetic. The use of multiple analgesics medications when compared to a single analgesic medication for reduction in pain post-operatively, allows more rapid post-operative recovery therefore allowing patients to resume normal activities of daily living sooner.[1, 11] Most enhanced recovery protocols as a result now include provisions for multimodal analgesia, in many cases beginning intraoperatively.

Exparel® is a formulation of bupivacaine (Pacira Pharmaceuticals, Inc., San Diego), offering extended-release bupivacaine tissue release, and thus prolonged analgesia. In the Exparel® formulation, multi-vesicular liposomes (MVL) encapsulate the bupivacaine medication. The tightly packed multi-lamellar vesicles that comprise an Exparel® unit have proven to provide longer term drug release compared to other technologies using uni-lamellar vesicles. This arrangement of vesicles within the Exparel®, spans tens of micrometers in diameter and slows degradation *in vivo,* allowing for greater sustainability of medication release lasting days as opposed to hours. Several randomized clinical trials have been completed with this novel medication leading to is approval by the Food and Drug Administration (FDA). The outcome measures included verbal pain scores, amounts and duration of use of post-operative opioid analgesics and patient satisfaction. In post market studies, researchers have conducted a wide range of surgical studies assessing the use of Exparel® for a variety of surgical procedures. Currently there are no prospective studies evaluating post-operative pain after roux-en-y gastric bypass. Of particular interest is the use of the circular EEA, which requires a larger incision site in the left upper quadrant, and is typically the site of the greatest operative pain.

A study conducted by Skolnik et al. assessing the use of Exparel® in ileostomy reversals indicates there was a statistically significant in reduction of post-operative opioid analgesic use, length of hospital stay, and maximal pain scores. A majority of the current studies support these findings, but the evaluation of Exparel® for post-bariatric pain is limited.

Roux-en-Y gastric bypass (RYGB) is a well-studied bariatric surgical procedure that is not

only a very effective procedure for weight loss, but is also associated with a reduction of significant co-morbid conditions. Roux-en-y gastric bypass operations involves the creation of two new anastomoses, the gastrojejunal anastomosis linking the gastric pouch to the roux limb, and the jejuno-jejunal anastomosis connecting the bypassed biliopancreatic limb with the distal Roux limb.[14] Nationally the circular EEA stapler is the most common technique to form the gastrojejunal anastomosis. This stapler is ~40mm in diameter, and is introduced through an incision in the left upper quadrant incision. This is the largest incision created and is typically the site of the most intense postoperative pain.[14] Given the location next to the costal margin, pain at this location can also lead to patients self-splinting, limiting lung expansion and putting them at risk for post-operative atelectasis, respiratory insufficiency or pneumonia.

Currently, there are no prospective trials for that examine post-operative pain management in patients undergoing laparoscopic roux-en-y gastric bypass utilizing a circular EEA staplers used to create gastrojejunal anastomosis. Objective data from such an investigation would serve to better direct patient care by providing needed information about the most appropriate medications to be used in reducing post-operative pain for this specific bariatric population, and resultant symptoms of pain and increased hospital resource use.

Aims and Hypothesis

Aim: To evaluate the efficacy in reducing post-operative pain with the use of Exparel® in comparison to bupivacaine injections in bariatric patients undergoing LRYGB with EEA stapler anastomosis at the incision sites.

Hypothesis 1a. Exparel® liposomal bupivacaine injected at the incisional sites prior to incision closure will reduce post-operative pain when compared to standard local analgesia using bupivacaine.

Hypothesis 1b. Exparel® liposomal bupivacaine injected at the incisional sites prior incision closure will reduce post-operative opioid analgesic use when compared to standard local analgesia using bupivacaine.

Hypothesis 1c. Exparel® liposomal bupivacaine injected at the incisional sites prior to incision closing will reduce unplanned readmission, and inquiries to medical providers regarding pain in the first 30 days post operatively compared to standard local analgesia using bupivacaine.

Materials and Methodology

Study Design

The study will be composed of 100, and will consist of two cohorts of 50 patients. The study cohort will include 50 patients who receive intraoperative Exparel® injections at the incision locations in addition to our standard multimodality post-operative analgesia. The control arm will include 50 patients who meet inclusion criteria but receive standard 0.25% bupivacaine and our standard multimodality post-operative analgesia. Patients will be randomized by REDCap™ database system in collaboration with Cleveland Clinic Pharmacy to receive either Exparel® or the control medication (0.25% Bupivacaine). Consent from patients will be obtained and documented by a dedicated research personnel prior to any enrollment.

Inclusion Criteria:
After Institutional Research Board (IRB) study approval, patients will be prospectively enrolled in to the study. The participants for this study will include bariatric patients who present at the Cleveland Clinic Bariatric Surgery Center of Excellence, over 18 years of age, fulfilling NIH criteria for bariatric surgery and will proceed with laparoscopic Roux-en-y gastric bypass with the use of EEA stapler anastomosis for the treatment of their obesity. Patients who fulfill the inclusion criteria and do not meet any of the exclusion criteria will be approached for participation. Patients will provide written personal signature on the consent/authorization form for enrollment in the study.

Exclusion Criteria:
Exclusion criteria includes age <18 years which is a contra-indication to laparoscopic roux-en-y gastric bypass, patients with previous history of roux-en-y gastric bypass, or patients undergoing other bariatric procedures. Patients on pre-operative opioid analgesics will also be excluded from participating in the study. If the physician feels that the safety of the patient is at risk the participant will be excluded from the study, patients will be additionally excluded. Participants unwilling and unable to return for required follow-up visits will also be excluded.

Methods

Phase I: Preoperative Procedures

All patients undergoing laparoscopic roux en Y gastric bypass will undergo pre-operative assessments. This includes appointments with internal medicine physicians specialized in care of the bariatric surgical population, nutrition counseling, psychological screening, demonstrated weight loss during a preoperative trial period, and additional evaluation and clearance by subspecialists based on co-morbid conditions. In addition patients have a complete history and physical examinations performed by or supervised by Dr. Matthew Kroh MD, and Dr. John Rodriguez, Staff Bariatric Surgeons that utilize the circular EEA technique. Consent for this study will occur during a preoperative visit.

Phase II: Operative procedure

The bariatric surgical procedure, (laparoscopic RYGB), will be performed at the Cleveland Clinic Main Campus Bariatric Surgery Center of Excellence. The gastro-jejunal anastomosis will be created through the use of a circular end to end anastomotic (circular EEA) stapler with a 3.5mm staple height (Covidien, Dublin, Ireland). Patients will be randomized to receive either Exparel (R) (liposome bupivacaine injection solution), or standard bupivacaine, ~0.25%. Standardized injection volumes and technique will be performed. The study coordinator and/or the co-investigators on this study will notify the operative team prior to incision time to remind them of participation in this study. Those administering the study medication will not be blinded to the administration, since the appearance between the medications is significantly different.

Phase Ill: Postoperative Procedures

Patients have an initial stay in the Post Anesthesia Recovery Area, and then are typically admitted to a nursing unit specializing in post-operative bariatric care. Patients will be followed by the surgical team while in the hospital, and all will receive the same multimodal anesthetic regimen Patients are advanced on a diet along a pre-determined schedule, starting usually on post-operative day 1.

At 24 hours a member of the research team will administer a 2-part questionnaire containing the VAS and the Revised American Pain Society Post-Operative Questionnaire (APS-POQ-R).[16] The latter is validated for assessment of the patient's experience of pain and it hindrance to daily activity in the post-operative period. The VAS and APS-POQ-R assessment will be administered at 48 hours only if the patient is not discharged on post-operative day 1. Assessors will be blinded to the medication that was administered in the operating room.

Following discharge from the hospital, standard follow up appointments are scheduled at 7-10 days, 1 month, 3 months, 6 months, and 12 months. Patients are monitored for adverse events from bariatric surgery, enumerated and standardized by the American Society of Metabolic and Bariatric Surgeons.[15]

. ED visits and readmissions, as well as phone calls to clinic for issues related to pain will be evaluated at 30 days postop via a retrospective chart review to assess patient healthcare usage after discharge. Assessors will be blinded to the medication that was administered in the operating room.

Chart review will be completed to determine the amount of intravenous and oral narcotic pain medication used during the hospital stay, converted to morphine equivalents. Chart review will also be completed to detect narcotic related adverse events, similar to those used in prior studies of Exparel®.**[17]**

All data will be collected in a password-protected REDCap™ customized for this project. Data points and schedule of assessment is provided in Table 2.

Study Protocol

CCF policy on the use of Exparel® will be followed throughout the study. Specific but not comprehensive points include;

- Use of Exparel® is limited to one per patient
- All safety guidelines as outlined in IOH policy on use of Exparel® will be followed
- All patients will be provided safety information concerning Exparel® on discharge

Local Analgesia Administration Technique for the Investigational Group (see Table 1)

- Dilute to final volume of 120mL
  (20mL Exparel® + 60mL Bupivacaine (0.25%) and 40mL 0.9% injectable saline)
- At the end of surgical procedure- inject 60mL around the left subcostal surgical site. Administer 40mL in the prefascial space, and 20mL at the dermal – subdermal junction
- inject 15mL at each remaining trocar site (4 trocar sites)= 60mL

Local Analgesia Administration Technique for the Control Group

- 60cc Bupivacaine (0.5%) and 60mL 0.9% injectable Saline (final concentration 0.25% bupivacaine)
- At the end of surgical procedure- inject 60mL around the left subcostal surgical site. Administer 40mL in the prefascial space, and 20mL at the dermal –subdermal junction
- Inject 15mL at each remaining trocar site (4 trocar sites)= 60mL

All injections will use a spinal needle, part of the stand operative equipment for this procedure, and be administered with a moving needle technique.

Table 1: Study Medication and Post-operative Multimodality Pain Regimen

	Investigational Group	Control Group
Intraoperative Analgesia		
Local anesthetic Administered as: ½ administered in the LUQ port site - 40 mL in prefascial space around the LUQ port - 20mL at dermal / subdermal junction of the LUQ port site ½ volume split among remaining ports	20cc Exparel® 60cc Bupivicaine (0.25%) 40cc Normal Saline Final volume: 120cc	60cc Bupivicaine (0.5%) 20cc Normal Saline Final volume: 120cc
IV analgesia	1000mg IV acetaminophen once + Additional medication administered by Anesthesia Providers	
Post-operative Analgesia		
If NPO	Ketorolac IV 30mg q6 hours x 48 hours Hydromorphone IV 0.2mg q4 hours prn	
After taking liquids	Acetaminophen po 1000 mg q8 hours Ketorolac IV 30mg q6 hours x 48 hours Roxicodone po 5-10 mg q4 hours prn Hydromorphone IV 0.2mg q4 hours prn	

All injections will be documented in the intra-operative report including areas injected, and amount of Exparel® or Bupivacaine used. Any adverse events are to be documented as well in the electronic medical record.

Pain assessment:

- First assessment at 24 hours post operatively using In Hospital Pain Assessment Questionnaire, including
  - Visual Analog Scale (VAS)
  - American Pain Society Post-Operative Questionnaire-Revised (APS-POQ-R)
- Second assessment at 48 hours post operatively with the same assessment questionnaires if the patient was not discharged on post-operative day 1.
- Retrospective chart review for Narcotic Associated Adverse Events (NAE)
  NAEs include:
  - Somnolence
  - Respiratory depression
  - Hypoventilation
  - Hypoxia
  - Dry mouth
  - n/v
  - constipation
  - Sedation
  - Confusion
  - Pruritus
  - Urinary retention
  - Post op ileus

Data Collection

As confidentiality of patient health records is of significant importance, the data obtained or recorded from this study will be stored in a REDCap (Research Electronic Data Capture) database developed by the principal investigator and co-principal investigator, research fellows, and the bariatric research support staff at the Cleveland Clinic. REDCap is a secure, web-based application designed to support data capture for research studies and among many functions, includes an intuitive interface for data entry, audit trails for tracking data manipulation, and automated export procedures with integration into statistical packages. Only researchers listed and approved on the study protocol will have access to the data. If data should need to be provided to investigators outside of the protocol, it will be provided without identifying information in order to protect the patient's privacy and remain in compliance with HIPAA. The database will be maintained throughout the approved duration of the project.

Table 2: Schedule of Assessments

Study Day/Time Point	Pre-op	Operative encounter (24, 48 hours post op)	7-10 days post op	1 month post op

Questionnaire				
VAS		I*		
APS-POQ-R		I*		
Satisfaction and healthcare utilization survey				
General Procedures				
Informed consent	I*			
Complete medical history	S			
Updated medical history		S	S	S
Medication history	S			
Medication changes		S	S	S
Vital Signs	S	S	S	S
Physical exam	S	S	S	S
Height	S			
Body weight	S	S	S	S
Body Mass Index	S	S	S	S
Laboratory Tests				
CBC	S			
Basic chemistry	S			

- S=Standard of Care; I=Investigational Procedures; *= no additional costs for Investigational Procedures.

APS-POQ-R

The following questions are about pain you experienced during the first 24 hours in the hospital or after your operation.

1. On this scale, please indicate the **least** pain you had in the first 24 hours:

0	1	2	3	4	5	6	7	8	9	10
no pain										worst pain possible

2. On this scale, please indicate the **worst** pain you had in the first 24 hours:

0	1	2	3	4	5	6	7	8	9	10
no pain										worst pain possible

3. How often were you in **severe** pain in the first 24 hours? Please circle your best estimate of the percentage of time you experienced severe pain:

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Never in severe pain										Always in severe pain

4. Circle the one number below that best describes how much pain **interfered or prevented you from**:

a. Doing activities in bed such as turning, sitting up, repositioning.

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

b. Doing activities out of bed such as walking, sitting in a chair, standing at the sink.

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

c. Falling asleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

d. Staying asleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

5. Pain can affect our mood and emotions. On this scale, please circle the one number that best **shows how much the pain caused you to feel**:

	0	1	2	3	4	5	6	7	8	9	10
a. Anxious	Not at all										Extremely
b. Depressed	Not at all										Extremely
c. Frightened	Not at all										Extremely
d. Helpless	Not at all										Extremely

6. Have you had any of the following **side effects**? Please circle "0" if no; if yes, please circle the one number that best shows the severity of each:

	0	1	2	3	4	5	6	7	8	9	10
a. Nausea	None										Severe
b. Drowsiness	None										Severe
c. Itching	None										Severe
d. Dizziness	None										Severe

Gordon, *et al. J Pain. 2011; 11(11): 1172-86*.

Visual Analog Pain Scale

How would you rate your current pain?

Place a mark along the line below

Interview at 1 Week and 1 Month Post-Operative Follow Up

1. How satisfied were you with your post-operative analgesia

Extremely dissatisfied	Very dissatisfied	Somewhat dissatisfied	Somewhat satisfied	Very satisfied	Extremely Satisfied

2. Were you readmitted to the hospital?

   Yes No

   If yes, for what reason? _____

3. Did you have any unplanned medical visits?

   Yes No

   If yes, for what reason? _____

4. Did you experience any health related problems during your recovery?

   Yes No

   If yes, what were they? _____

5. Did you contact a medical provider about your recovery, apart from your scheduled post-operative visits?

   Yes No

   If yes, for what reason? _____

Statistical analysis
Descriptive statistics will be computed for all variables. These include means, ranges, standard deviations, and percentiles for continuous variables and also frequencies and percentages for categorical variables. Data will be separated into two groups; investigational group and control group. Data will be presented as mean ± standard deviation, median [interquartile range] or N (%). All analyses will be performed using SAS (version 9.2 or higher, The SAS Institute, Cary, NC) and R (version 2.13.1 or Higher, The R Foundation for Statistical Computing, Vienna Austria). A $P < 0.05$ will be considered statistically significant Results will be compared within each cohort and between cohorts.

Power analysis
This power analysis was calculated for the primary aim of the study to compare post-operative pain reduction between both cohorts. Calculations were made based on results in the Butz et al. paper involving the use of the VAS scale in postoperative pain in breast reconstruction. Power was calculated assuming the use of a two-sample t test to compare mean VAS levels between Exparel® patients and patients given the standard of care treatment. The actual difference in means was assumed to be 1.5 mm and pooled standard deviation was varied across a range from 1 mm to 3 mm. For standard deviations similar to those seen in the Butz article, 50 patients are calculated to give > 85% power to detect a 1.5 mm difference in mean VAS at a standard deviation of 2.6 mm.

Based on these calculations, a sample size of 50 patients per group is adequate under the conditions seen in the reference paper- a pooled standard deviation of about 2 mm and a difference in means of about 1.5mm. However, we see from the other conditions explored that the adequacy of this sample size (defined as having ≥ 80% power to detect a difference) is somewhat sensitive to either the true difference in means being less or the standard deviation larger.

Timeline and Feasibility
We fully expect to achieve our objectives upon completion of the funding period based on statistical and clinical resources available through the Digestive Disease and Surgery Institute, and Department of Quantitative Health Sciences.

Risk/Benefit Analysis

Benefits
Participation in this study may help to improve post-operative pain. There is no guarantee that all patients will benefit by participating in this research study. Participation in this study may provide information that may help other people in the future.

Risks
There may be risks or side effects related to the study drug that are unknown at this time. Patients and IRB will be notified of any significant new findings that become known that may affect the patient's willingness to continue in the study. There are no additional risks related to this beyond those which would be routinely discussed related to surgery. The treating physician will counsel subjects regarding the surgical risks related to each procedure as part of obtaining informed consent.

Complications
Any complications, anticipated or unanticipated, will be monitored until they are resolved or explained.

Protocol Changes
Any changes to the study protocol will be reviewed and approved by the Cleveland Clinic IRB prior to implementation.

Study Termination
The investigator may terminate this study at any time. All data collected prior to termination of study can be used for analysis.

Data Monitoring and Coordination Procedures
The study investigator or his designee will monitor the study by frequent communications with all personnel engaged in the study to assure that the study is carried out according to protocol. Data will be entered into a database to facilitate data analysis. Proper precautions will be taken to ensure the safety of patient information. The Principal Investigator or his designee will monitor the study at least once a year for data quality, subject recruitment, accrual, and retention, outcome and adverse event data, assessment of scientific reports or therapeutic development, results of related studies that impact subject safety, and procedures designed to protect the privacy of subjects.

IRB Reporting
Events requiring prompt reporting to the IRB will be done so in a timely manner. At the time of continuing review, the following information will be provided: 1) summary of cumulative adverse events (if any); 2) assessment of external factors (i.e. scientific reports, therapeutic developments, results of related studies) that impacted the safety of subjects; and 3) any changes to the risk-benefit ratio.

Consent Forms
Each patient, prior to evaluation, will sign a consent form. Copies will be distributed as follows: the original copy will be retained by the study coordinator, and one copy will be given to the patient.

Study Records and Reports
Investigator Records
The investigator is responsible for the preparation, review, and retention of the records listed below:

- all correspondence that pertains to the study,
- source documents containing clinical results,
- documentation of date and reason for any deviation from protocol

- All applicable essential documents, as defined by Sections 8.2-8.4 of ICH E6 Guidance on Good Clinical Practice

Information Use

Clinical information gathered from this study may be formalized in a manuscript and submitted for presentation or publication in a medical journal.

Local/Institution Review Board

The protocol for this investigation will be reviewed and by the Institutional Review Board (IRB).

Available Resources

There will be no dedicated space or equipment for the procedures specific to this investigation, however all shared facilities and equipment will be available. Procedures included in this study will occur at the standard facilities. At the Cleveland Clinic, these procedures take place in the operating theaters/suite. A research coordinator will be responsible for consenting patients prior to their involvement in this study. The surgical procedures for this study will be performed by Dr. Kroh, Director of Surgical Endoscopy, and Dr. Rodriguez.

Office: Dr. Rodriguez and support staff have adequate office and clinic space in the Digestive Disease Institute.

Operative theaters: Dr. Rodriguez and his co-investigators will have access to the Cleveland Clinic's operative rooms in order to perform the operative procedure. These operative rooms are fully equipped for the desired bariatric procedure.

Statistical Support: The Cleveland Clinic Digestive Disease and Surgery Institute has a dedicated biostatistician that will statistically support for the analysis associated with this study.

Communication: Additional areas that are available to support this study include a conference room and library space with both teleconferencing and videoconferencing capabilities.

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