Title: Randomized Controlled Trial Investigating Use of Liposomal Bupivacaine in Bariatric Surgery.

Study Key Name Liposomal Bupivacaine in Bariatric Surgery

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ABBREVIATIONS AND DEFINITIONS OF TERMS

MMC	Montefiore Medical Center
LP	Liposomal Bupivacaine
LSG	Laparoscopic Sleeve Gastrectomy
LRYGB	Laparoscopic Roux en y Gastric Bypass
PCA	Patient Controlled Analgesia
TAP	Transversus Abdominis Plane
LB	Liposomal Bupivacaine
RB	Regular Bupivacaine

ABSTRACT

Context:

There has been increasing effort to reduce the use of opiates in the general population. The obese population, and in particular those undergoing bariatric surgery, represent an especially high-risk group for the adverse effects associated with opiate use.

The aim of this study is to perform a randomized controlled trial for patients undergoing bariatric surgery, comparing the need for opiates with and without administration of a transversus abdominis plane (TAP) block using the long acting local anesthetic, liposomal bupivacaine (Exparel®). From this study, we will investigate whether use of long acting local anesthetic can reduce the need for opiates in the bariatric population.

Objectives:

- To determine the effect of using long acting local anesthetic for a transversus abdominis plane block on opiate use in the bariatric population

Study Design:

- A prospective randomized controlled trial investigating the use of long acting local anesthetic for transversus abdominis block in patients undergoing bariatric surgery at Montefiore Medical Center.

Setting/Participants:

- This is a single center study of patients undergoing bariatric surgery in the Department of Surgery at Montefiore Medical Center.

Study Interventions and Measures:

- Main study outcome measures will include but not limited to: opiate use (adjusted for opioid equivalence).

- Secondary study outcome measures will include: 24-hour composite paint scores, length of stay, respiratory complications (pneumonia, atelectasis), venous thromboembolic event, myocardial infarction, nausea, vomiting, time to adequate oral intake (3 ounces each hour), and time to ambulation.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

More than one third of the population in the United States is obese. Over 190,000 people have undergone bariatric surgery each year for the last 2 years. The most common procedures performed are the laparoscopic sleeve gastrectomy (LSG) and laparoscopic roux en y gastric bypass (LRYGB). Pain management is essential for prevention of post operative respiratory complications. Obtaining adequate analgesia, particularly judicious administration of opiates, can be a double-edged sword. While opiates provide a large part of the post operative pain regimen that is essential to achieve early ambulation and accommodate adequate ventilation and chest excursion, it also acts as a respiratory depressant and holds strong addictive potential. The aim of this study is to perform a prospective randomized controlled trial of patients undergoing bariatric surgery examining opiate use and pain control in those who undergo intraoperative TAP block with liposomal bupivacaine (LB) or regular bupivacaine (RB) compared to those who receive standard postoperative pain regimens.

1.2 Compliance Statement

This study will be conducted in full accordance of all applicable Montefiore Medical Center Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The Montefiore Medical Center IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

1.3 Relevant Literature and Data

Increased opiate use is associated with increased rates of delirium, ileus, urinary retention, and respiratory depression. Transversus abdominis plane (TAP) block is a safe and effective approach to achieve optimum pain control and reduce the use of opiates in patients undergoing major abdominal surgery. A randomized controlled trial comparing TAP block with bupivacaine and a standard post-operative analgesia regimen demonstrated a reduction in visual analog pain scales throughout the initial 24 hour post-operative period, as well as a 4-fold reduction in the amount of morphine required by patients. All of the patients included in this study were undergoing exploratory laparotomy and bowel resection (McDonnell et al).

Numerous studies have compared the use of liposomal bupivacaine and non-liposomal anesthetic for the use of TAP block with data indicating a benefit with the use of liposomal bupivacaine. Fayezizadeh et al. compared TAP block in patients undergoing abdominal wall reconstruction with historical cohorts. This study demonstrated improved pain scores and decreased narcotic consumption with the TAP block. Keller et al. performed a prospective pilot study comparing pain scores and narcotic use with and without TAP block in patients undergoing colorectal surgery. They found that the group who underwent TAP block had decreased pain scores, decreased narcotic use and shorter length of stay compared with the control group. Hutchins et al. compared the use of liposomal bupivacaine with nonliposomal local anesthetic in patients undergoing hysterectomy. This trial was a prospective randomized controlled observer blinded study. It demonstrated decreased total opioid use in the first 72 hours after surgery as well as decreased pain scores.

Morbidly obese patients due to high incidence of obstructive sleep apnea (OSA) are predisposed to opioid induced airway obstruction and thus frontline high ceiling analgesics (opioids) have concerns based on safety in their liberal use (Alvarez et al). Multiple studies have demonstrated a decrease in post-operative pain and thus diminished opioid consumption post-intervention. The morbidly obese bariatric population, who are at a particularly higher-risk for opioid induced complications such as apneic events and possible cardiac death, would benefit from a post-surgical analgesia regimen that would decrease or eliminate said risks.

2 STUDY OBJECTIVES

- The aim of this study is to perform a prospective randomized controlled trial to investigate the effect of performing a TAP block using long acting local anesthetic on opiate use and pain control in the bariatric population. From this data we propose to determine if we can adequately and safely forego implementation of PCA and reduce the overall use of opiates, while providing sufficient analgesia.

2.1 Primary Objective

- To determine if the use of long acting or regular acting local anesthetic for TAP block will have an effect on the use of opiates in patients undergoing bariatric surgery at MMC.

2.2 Secondary Objectives

- To identify associations between demographic factors, such as age, race, types, pathology findings with outcomes.

- To identify any difference in 24 and 48-hour composite pain scores, the length of stay, incidence of cardiac or respiratory complications, or incidence of venous thromboembolic events between the three groups.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

- Prospective randomized controlled trial of patients undergoing bariatric surgery at Montefiore Medical Center.

- This will only include inpatient data

3.2 Study Duration, Enrollment and Number of Sites

3.2.1 Date Range of Study

- Cases included will take place at MMC between 01/01/2018 and 12/31/2018 over a 1 year period.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

- This prospective study will enroll patients at a single study site of MMC (Moses Division).

- We plan to enroll 219 patients/subjects (73 patients for each arm)

3.3 Study Population

3.3.1 Inclusion Criteria

1) Obese patients undergoing bariatric surgery (LSG or LRYGB)
2) Patients 18 years of age and older
3) Surgical treatment between 01/01/2018 and 12/31/2018 over a 1 year period

3.3.2 Exclusion Criteria

1) Patients under the age of 18 years old
2) Patients taking any opiates within 30 days of enrollment in the trial
3) Patients with a history of chronic pain.
4) Patients taking pregabalin or gabapentin.
5) ASA IV
6) Prior laparotomy
7) Body Mass Index $\geq$ 60 kg/m^2
8) History of cardiac arrhythmia
9) History of Seizure
10) Psychiatric Diagnosis currently on antipsychotic medication
11) Pregnancy
12) Patients who are breastfeeding.

4 STUDY PROCEDURES

Patients will be randomized to either receive an intraoperative TAP block with LB, an intraoperative TAP block with RB, or no TAP block. All patients will receive standard post-operative analgesia regimen. This includes fentanyl PCA at 10mcg every 10 minutes for the first 24 hours. Acetaminophen with codeine elixir (360mg/36mg) by mouth every 4 hours, ketorolac 30mg intravenously every 6 hours and dilaudid 0.4mg intravenously every 3 hours are for breakthrough pain are ordered post- postoperatively and continued until discharge.

The solution used to perform the TAP block with LB will comprise of 20mL of liposomal bupivacaine solution, 30mL of 0.25% bupivacaine, and 100mL of normal saline. The solution used to perform the TAP block with RB will comprise of 50mL of 0.25% bupivacaine and 100mL of normal saline. The TAP block is performed under laparoscopic visualization. An initial 5mm optical trocar is placed. The peritoneum and then TAP are then infiltrated with the local anesthetic under direct visualization. Skin incisions are infiltrated and trocar sites are anesthetized prior to placement of ports. Analog pain scale will be used to determine the pains score of the subjects as they emerge from general anesthesia (Time 0 hours). Pain scores will be recorded every 4-6 hours

by the nursing staff as reported by the patients. Patients will be monitored for secondary post-operative complications up to the 2-week mark following intervention.

4.1 Data Variables and Sources

4.1.1 Subject Recruitment

All subjects will have undergone the standard rigorous preoperative evaluation by our multidisciplinary team. Risks and benefits will be explained to subjects in our clinic and consent will be obtained by our research coordinator during the preoperative visit.

4.1.2 Data sources

The subject will be the primary source of demographic data and past medical history. The electronic medical record will also be reviewed prior to offering enrollment to ensure that patients meet all of the inclusion criteria and do not meet any of the exclusion criteria. Pain scores and quantity of opiates used will be documented by nursing staff.

4.2 Measures to Avoid Bias

All patients enrolled in the study will be blinded. The TAP block is performed intraoperatively, and there is no outward sign of injection that would allow the patient or person examining the patient to tell whether the patient had received the TAP block. The surgeon will not be blinded. The liposomal bupivacaine has a distinct cloudy appearance that would be difficult to replicate otherwise. In addition, as part of the TAP block, the transversus abdominus plane is hydrodissected by the local anesthetic. Injection/hydrodissection using a placebo (no local anesthetic) may increase pain and therefore has been excluded from the control arm of the study. Anesthesia will be blinded. The anesthesiologist will leave the room and be replaced by another anesthesiologist for the duration of the block. Once an appropriate amount of time has lapsed, the attending anesthesiologist will return to the room. This is done so as to avoid bias in administration of opiates intraoperatively by anesthesia depending on which arm of the study the patient is on. In addition, the nursing staff will be blinded, which is important as they will be recording the pain scores as per nursing protocol. The research staff collecting data will not be blinded. Pharmacy will document in the orders “Study Drug – TAP Block.” This will allow researchers to look through the record and know the patient was enrolled in the study, but it will not allow them to know which arm of the study the patient was in.

All relevant chart information and collection will be standardized to avoid bias. Before commencing chart reviews, all relevant terminology will be determined and standardized. The specific sources of relevant information will be identified, as will their location within the documents. During the review process, regular meetings between the Principal Investigator and chart reviewer will be held to discuss any modifications to the standard that may be needed. Five percent of charts will be selected at random and reviewed by a third party who is trained in the standardized terminology and sources of information in order to validate the original review for accuracy.

5 STATISTICAL CONSIDERATIONS

5.1 Primary and Secondary Outcomes

The primary outcome will be quantity of opiates used in terms of morphine equivalents. Secondary outcomes will include 24-hour composite pain scores, length of stay, respiratory

complications (pneumonia, atelectasis), venous thromboembolic event, myocardial infarction, nausea, vomiting, time to adequate oral intake (3 ounces each hour), and time to ambulation. Pain scores will be recorded by nursing staff using the universal pain assessment tool.

5.2 Sample Size and Power

The hypothesis for this study is that the 48 hour opioid consumption is different in one of the three groups. The study is powered to show a minimum clinically significant reduction of 30% in opioid usage compared to the control group (placebo group) 20% between the regular bupivacaine groups. According to our clinical audit, the mean (standard deviation) of amount of opioids used by patients undergoing these surgeries is 23.3±14 mg morphine equivalents. Based on a two-sided alpha of 0.05 and 20% Type II error, 200 subjects need to be studied to disprove the null hypothesis. Additionally, to accommodate for attrition and missing data we plan to increase our sample size by 10%, a total of 219 subjects will be randomized.

5.3 Data analysis plan

Demographic and clinical characteristics such as (age, gender, type of surgery, medications, ASA status, co- morbidities, etc.) between the three study groups will be compared using one-way ANOVA or a non-parametric Kruskal Wallis test. Chi-square or Fisher's exact tests for categorical variables to ensure that randomization is appropriately implemented. The primary outcome of the study the opioid consumption at 48 hours will be analyzed using one-way ANOVA or a non-parametric Kruskal Wallis test. Mixed model analysis will be used to examine the effect of treatment on change in pain scores between the groups at 24 hours and 48 hours. All categorical variables such as, post-operative nausea and vomiting and any other clinically important medical conditions will be compared using chi-square or Fisher's exact tests.

5.4 Randomization

The research data collector will be responsible for the randomization. Subjects will be randomized in a1:1:1 ratio to receive LB as a TAP block infiltration or RB as a TAP block infiltration or no TAP block infiltration.

6 STUDY ADMINISTRATION

6.1 Data Collection and Management

Nursing staff will document pain every 4-6 hours using the patient reported composite measure pain score, with a total range of 0 to 10, with 0 being the absence of pain, 1 being the least amount of pain and 10 being the highest amount of pain. Data will be obtained from patients and the electronic medical records. Privacy and security will be maintained by minimizing the amount of identifiable data as much as possible. All information will be compiled in Excel spreadsheets that are password protected.

All necessary identifiers will be used only to identify the relevant source documents (as described above). Following this, surrogate numbers will be given to identify the patients for data analysis. All identifiers will be deleted from the file. This information will remain in a separate password protected file that served as the initial list of cohort patients to be searched until after completion of the study period and analysis, at which point it will be deleted.

6.2 Confidentiality

All data and records generated during the process of this study will remain confidential in accordance with all Institutional and HIPAA policies on subject privacy. All documents will be used by the Investigator and other personnel solely for the purposes of this study. All safeguards to maintain subject confidentiality are described above ("6.1 Data Collection and Management"). No information will leave Montefiore in the event that an investigator leaves during the duration of the study.

6.3 Regulatory and Ethical Considerations

6.3.1 Risk Assessment

The risks of the proposed study include any of the risks with bariatric surgery in general. The following are risks of the proposed intervention: hematoma at site of injection, anaphylaxis, arrhythmia, vascular/visceral/nerve injuries, block failure, seizures. There is also an anticipated risks of breech of privacy and confidentiality. As explained in Data Collection and Management, extreme care will be taken to maintain the patient's privacy, security, and confidentiality.

6.3.2 Potential Benefits of Study Participation

The main benefit of this study would be to reduce the amount of narcotics utilized by the bariatric population. As explained previously, this population is at particularly high risk of respiratory complications associated with excessive opiate use.

6.3.3 Data Safety Monitoring Plan

The investigators will closely monitor the data safety as described in Einstein's IRB Data Safety Monitoring Policy. We have also established a data safety monitoring committee (DSMC) to review the protocol on an ongoing basis for adverse events that will report to the IRB immediately should any serious adverse event occur. All serious unanticipated adverse events will be reported to the IRB and DSMB in a timely manner. In the event of unanticipated serious adverse event, including death, continuation of the study will be at the discretion of DSMB and IRB. The DSMB meeting will only be held in the event of serious adverse events. The DSMC will be comprised of an anesthesiologist (Dr. Mike Ruffino), a surgeon (Dr. Scott Melvin), an internist (Dr. Regina Lee), and a statistician (Dr. Patricia Friedman) who are independent of the study. These individuals are completely independent from this project and have no conflict of interest.

6.4 Informed Consent

This study represents a prospective randomized controlled trial of patients undergoing bariatric surgery at MMC. All patients will be explained the risks and benefits of surgery and will have the option to opt out of the study with no effect on delivery of their care. Demographic information will be obtained, such as name, medical record number, age and gender, but beyond this no more specific identifying information is necessary and will be left out. Once possible, all identifiers will be removed from our databases. Study results will not include any identifying information, and privacy will be protected as previously described.

7 PUBLICATION

Once the study is complete and conclusions are made, a manuscript will be submitted to a relevant journal for publication.

8 REFERENCES

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Hutchins et al. Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic assisted hysterectomy: A prospective randomized controlled study. *Gynecol Oncol* (2015) 3:609-613.

Keller et al. Pilot study of a novel pain management strategy: evaluating the impact on patient outcomes. *Surg Endosc* (2016) 30: 2192-2198.

Mc Donnell et al. The Analgesic Efficacy of Transversus Abdominis Plane Block After Abdominal Surgery: A Prospective Randomized Controlled Trial. *Anesth Analg* (2007) 104: 193-197.

9 APPENDIX

9.1.1 STUDY-MASTER LIST

Study number	Patient's name	Patient's medical record number	Operative Procedure	24-Hour Composite Pain Score	Overall Opioid Use in morphine equivalents
1					
2					
3					
4					
5					

9.1.2 DATA COLLECTION SHEET

Patient study number _____

Patient gender: male / female

Race: Caucasian____, African American____, Asian____, Hispanic (white)____ Other_____

Patient's age ____

Patient's weight /BMI____

Procedure ____

Comorbidities ____

Pathology ____

Outcomes:

Overall narcotic use ____

24-Hour composite pain score ____