TAP Block Study

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Study Title: Single Blinded Randomized Trial of Transversus Abdominis Plane Block Using Liposomal Bupivacaine in Metabolic and Bariatric Surgery Patients

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Background, Rationale, and Context

The transversus abdominis plane (TAP) block was described in 2007 using an ultrasound to inject local anesthetic between the internal oblique and transversus abdominis muscles where the sensory nerves of the abdominal wall travel [1]. The TAP block can also be performed by the surgeon with laparoscopic guidance. TAP block has been shown to provide analgesia after abdominal surgery, decreasing opioid use, and is widely accepted into practice [2]. TAP block has become a cornerstone in enhanced recovery after surgery programs, as well as part of multimodal analgesia, and opioid reducing efforts nationwide. A recent meta-analysis of Randomized Controlled Trials (RCT) comparing TAP block with bupivacaine or ropivacaine to no TAP block in bariatric surgery showed reduced postoperative nausea and vomiting and time to ambulation [3]. Liposomal bupivacaine compared to plain bupivacaine has been touted to provide a longer duration of analgesia (up to 72 hours) by slowly releasing the anesthetic agent into local tissue. A recent systematic review comparing liposomal bupivacaine to conventional local anesthetic agents in regional anesthesia, including TAP blocks, showed conflicting results so no definitive conclusions could be made [4]. It is unclear if liposomal bupivacaine is superior to plain bupivacaine for TAP blocks in bariatric surgery. Our study would be the first RCT comparing laparoscopic TAP block with liposomal bupivacaine vs plain bupivacaine in a bariatric surgery population.

Objectives

Compared to only Bupivacaine administered via TAP block, we will investigate the analgesia effects to patients undergoing metabolic and bariatric surgery receiving TAP block with a Liposomal Bupivacaine mixture.

Primary Objective**:** To determine if patients undergoing metabolic and bariatric surgery receiving TAP block with a Liposomal Bupivacaine results in pain scores, as measured by visual analogic scale (VAS), that are equivalent compared to patients receiving TAP block with Bupivacaine only.

Primary Hypothesis:

1) Lower values of the outcome variable VAS are desirable, and the hypothesis is listed below –

Hypothesis 1. 1

H_0: $\mu_E - \mu_S \geq \delta$ (Study group is different compared to the active control group by δ or more)

H_1: $\mu_E - \mu_S < \delta$ (Study group is equivalent to the active control when difference is within prespecified δ)

Where μ_E, μ_S are the population means for the outcome VAS measured at 24 hours after surgery for the study group (E) and the standard (S) active group, respectively

δ is non-inferiority margin, specified in advance based on clinical judgement. Based on our clinical experience, δ = 1.5

Secondary Objectives: Compared to TAP block with Bupivacaine only, we will compare opioid consumption, and other effect differences to patients undergoing metabolic and bariatric surgery receiving TAP block with Liposomal Bupivacaine.

Secondary Hypotheses

Hypothesis 2.1 – Patients undergoing metabolic and bariatric surgery receiving TAP block with Liposomal Bupivacaine results in less opioid consumption before hospital discharge /during the first 48 hours postoperatively as measured in morphine equivalents (mg) compared to patients receiving simply TAP block with Bupivacaine only.

Hypothesis 2.2 - Patients undergoing metabolic and bariatric surgery receiving TAP block with Liposomal Bupivacaine results in pain score as measured by visual analogic scale (VAS) at 12 hours after surgery that are equivalent compared to patients receiving TAP block with Bupivacaine only.

Exploratory objectives: We will explore other effects, including pain score at 48 hours, and 72 hours after surgery, total opioid consumption required post op during their one-week post op visit as measured in morphine equivalences.

Methods and Measures

Design

This study is a 2-arm parallel single blinded randomized equivalency, single-center, clinical trial. Patients will be blinded to type of TAP block used.

Setting

This study will take place at Atrium Health, an academic medical center.

Subjects selection criteria

Inclusion Criteria

To be eligible for enrollment in this study, participants must meet all the following criteria:

1. Adult, age > 18 years
2. Participants who can give written informed consent and willing to comply with all stud-related procedures.
3. Patients undergoing primary sleeve gastrectomy or roux-en-y gastric bypass

Exclusion Criteria

1. Patients undergoing duodenal switch procedures
2. Patients undergoing concomitant hiatal hernia repair or ventral hernia repair or cholecystectomy at time of primary metabolic surgery
3. Patients with chronic opioid use

Sample Size

The number of patients required in each group is determined from a power analysis based on primary hypothesis.

In this study, based on our clinical experience, we assume standard deviation for each group is 3, the margin of equivalence is 1.5 on NRS, and the true difference between the two groups is 0 on the NRS. Group sample size of 88 from each group achieves 90% power to detect our prespecified equivalence margins, with alpha of 0.05. Assuming a 20% dropout or withdrawal based upon previous experience, 106 subjects per group will be required.

Interventions and Interactions

There will be two groups: (1) active control and (2) study group. Active control group patients receive TAP block with a Bupivacaine only mixture, containing 50 mL 0.5% Bupivacaine, and 100 mL normal saline solution. Study group patients will receive TAP block with a Liposomal Bupivacaine mixture, containing 20 mL Liposomal Bupivacaine, 30 mL 0.5% Bupivacaine, and 100 mL normal saline solution. TAP block technique will be standardized using subcostal as well as anterior axillary line as landmarks, injecting down to level of T10, using laparoscopic-guided approach. TAP block will be administered at the start of every case, after the first port is placed upon laparoscopy. Type of anesthesia administered will also be standardized including the use of narcotics, lidocaine, inhalational anesthesia and Ketamine.

Randomization schedules will be generated by SAS 9.4 (SAS Institute Inc., Cary, NC) by using a masked block randomization procedure. Eligible patients will be randomized with a 1:1 ratio between the 2 groups of patients receiving TAP block Exparel mixture or simply bupivacaine administered via TAP block. Research Electronic Data Capture (REDCap) randomization

module will be used to manage randomization and allocate treatment groups. The allocation sequence will be concealed with application of the REDCap.

Outcome Measure(s)

Primary Outcome measures

1. Pain score at 24 hours post-operative, using visual analogue scale (VAS), ranging from 1 to 10. One indicates no pain, and 10 indicates the worst pain one could image.

Secondary Outcome Measures

1. Pain scores at 12 hours, 48 hours, and 72 hours post-operatively.
2. Morphine milligram equivalences consumed during hospital stay
3. Morphine milligram equivalences prescribed and consumed as measured at one week follow up clinic visit
4. Post-operative nausea and vomiting (PONV) measured by a numerical score (1: no nausea or vomiting, 2: some nausea no vomiting, 3: nausea and vomiting)
5. Length of stay in hours
6. Patient satisfaction score

These parameters will be scored via SeamlessMD on a phone application, as well as paper and pen on a standardized reporting form for patients less comfortable using technology. Data will also be collected from patient electronic charts.

Analytical Plan

Equivalency test with priori specified non-inferiority region will be used to assess primary outcome variables.

Descriptive statistics (mean, range, percentage, median, etc.) will be used to assess the quality and accuracy of the administrative and clinical data. Means with standard deviations or medians with interquartile range (IQR) will be reported for continuous variables and percentages for categorical variables. Missing data will be evaluated prior to data modeling. General linear regression, or other generalized linear regression models will be used to compare the outcomes between the two groups with both univariate or multivariate analyses. Potential confounders will be identified with univariate analysis. For univariate analyses, a Student's t-test or Wilcoxon two-sample test will be used for continuous variables, and chi-square test for categorical variables against the primary and secondary outcomes. Both unadjusted and adjusted odds ratio (OR) with

corresponding 95% confidence interval (CI) will be reported. Two-tailed p values will be calculated for all tests, and $p< 0.05$ is considered statistically significant. All data will be analyzed using Statistical Analysis Software, version 9.4 (SAS Institute Inc., Cary, NC).

There are no plans for interim data analyses. Analyses will be conducted according to per-protocol (PP) principle.

Human Subjects Protection

Subject Recruitment Methods

Patients who are scheduled for sleeve gastrectomy or roux-en-y gastric bypass will be identified and recruited for the study at the Atrium Health Weight Management clinics during their preoperative visit. The bariatric surgeons and bariatric surgery fellows will do the recruiting, and patients will be contacted directly face to face during the preoperative visit about the study. Patients will also receive a written flyer containing information about the study during the preoperative visit. As all qualifying patients will be informed about the study during the preoperative visit, access to participation among women and minorities will depend on how many of these patients undergo sleeve gastrectomy or roux-en-y gastric bypass at our institution. Subject's privacy will be protected by storing records of Protected Health Information in locked facilities or password protected computers. Data will be stored on a password protected computer of the investigator and in a password protected RedCap database.

Informed Consent

Signed informed consent will be obtained from each subject. The investigators as well as the other bariatric surgeons and bariatric surgery fellows will obtain informed consent at the Atrium Health Weight Management clinics during the preoperative visit.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed (state the anticipated time the data will be destroyed, e.g. three years after closure of the study, and the method of destruction), consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data

password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

References:

1. McDonnell JG, O'Donnell BD, Farrell T, et al. Transversus abdominis plane block: a cadaveric and radiological evaluation. Reg Anesth Pain Med. 2007;32:399–404

2. Mukhtar K, Singh S. Transversus abdominis plane block for laparoscopic surgery. Br J Anaesth. 2009;102:143–4.

3. Hytham K.S. Hamid, Amjed Y. Ahmed, Alan A. Saber, Sameh H. Emile, Mohamed Ibrahim, Jaime Ruiz-Tovar. Transversus abdominis plane block using a short-acting local anesthetic reduces pain and opioid consumption after laparoscopic bariatric surgery: a meta-analysis, Surgery for Obesity and Related Diseases. Volume 16, Issue 9. 2020, Pages 1349-1357

4. Jin Z, Ding O, Islam A, Li R, Lin J. Comparison of liposomal bupivacaine and conventional local anesthetic agents in regional anesthesia: A systematic review. Anesth and Analg. 2021; 132 (6): 1626-34.

Appendix

1. Consent form
2. Copy of Seamless MD Daily Health Check surveys