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Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Laparoscopic Transversus Abdominis Plane Block in Gastric Bypass Surgery

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Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Laparoscopic Transversus Abdominis Plane Block in Gastric Bypass Surgery

LapTAP Trial

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ABSTRACT

INTRO: Evaluating the efficacy of a laparoscopically-guided, surgical transversus abdominis plane (TAP) and rectus sheath (RS) block in reducing analgesic consumption while improving functional outcomes in patients undergoing laparoscopic bariatric surgery.

METHODS: 150 morbidly obese patients undergoing elective laparoscopic Roux-En-Y gastric bypass (LRYGB) for obesity will be recruited to this double-blinded, placebo-controlled Randomized Control Trial from a Bariatric Center of Excellence over a period of six months. Patients will be electronically randomized on a 1:1 basis to either an intervention or placebo group. Those on the intervention arm will receive a total of 60 mL ropivacaine, divided into four injections: two for TAP and two for RS block under laparoscopic visualization. The placebo arm will receive normal saline in the same manner. A standardized surgical and anesthetic protocol will be followed, with care in adherence to the Enhanced Recovery after Bariatric Surgery (ERABS) guidelines.

ANALYSIS: Demographic information and relevant medical history will be collected from the 150 patients enrolled in the study. Our primary efficacy endpoint is cumulative postoperative narcotic use. Secondary outcomes are peak expiratory flow (PEF), Post-operative pain score and the 6-minute walk test. Quality of recovery will be assessed using a validated questionnaire (QoR-40). Statistical analysis will be conducted to assess differences within and between the two groups. The repeated measures will be analyzed by a mixed modeling approach and results reported through publication.

ETHICS AND DISSEMINATION: Ethics approval was obtained through our institutional research ethics board and the study results, regardless of the outcome, will be reported in a manuscript submitted for a medical/surgical journal.

ARTICLE SUMMARY

Strength and Limitations

Strengths:

- RCT conducted at a Bariatric center of Excellence.
- Large Number of Patients.
- Standardized Surgical and Anaesthetic technique.
- First RCT to assess TAP and Rectus Sheath Blocks in Bariatric Patients.
- Reproducibility and patient involvement.

Limitations:

- Block Administered at the end of the case instead of beginning as suggested in some of the new evidence.

Study Protocol

1. *Trial Title and Protocol Number*

Title: Randomized, Double-Blinded, Placebo-Controlled Trial of Laparoscopic Transverse Abdominis Plane (Lap TAP) and Rectus Sheath Block in elective Gastric Bypass Surgery

Protocol Number: **20170749-01H**

ClinicaTrials.gov registration number: NCT03367728

Universal Trial Number (UTN): U1111-1206-9983

Background and Rationale

2.1 Background

Management of post-operative pain remains a major challenge and an area of continued research. Effective pain control, apart from providing general patient comfort, is critical for a variety of clinical reasons. It leads to early ambulation and improved respiratory function, which significantly reduces the risk of post-operative complications such as pulmonary embolus or pneumonia, as well as early discharge.

Post-operative pain management was typically opioid-based; however, post-operative opioid use may be associated with increased risk of respiratory depression and sedation. It is therefore desirable to implement opioid-sparing multimodal analgesia to achieve satisfactory pain control while reducing post-operative opioid requirements and their side-effects.

Rational pain management is a particularly pertinent issue in the patients with morbid obesity (M.O.). The pathophysiology of obesity, the high prevalence of obstructive sleep apnea, and high susceptibility to respiratory depression amongst patients with M.O. make safe analgesic management especially difficult. These individuals are at high risk of post-operative adverse respiratory events, nosocomial infections, cardiovascular complications, and pulmonary emboli (the second leading cause of death in the bariatric surgery population).

Given the increasing number of patients with morbid obesity presenting for elective weight loss surgery, it is important to understand and optimize the analgesic requirements of this patient population. However, there are limited evidence-based recommendations and no ideal analgesic regimen exists for patients with M.O. Current recommendations include use of step-wise severity-based opioid- sparing multimodal analgesia. It is possible that including local anesthetic blocks will further reduce pain, opioid analgesic consumption and side-effects from pain management (sedation, confusion, nausea & vomiting etc.) at-risk patient population.

The aim of this study is to evaluate the efficacy of a laparoscopically-guided, surgical transversus abdominis plane (TAP) block and rectus sheath block in reducing post-operative opioid consumption and improving outcomes in patients undergoing laparoscopic gastric bypass surgery. The results of

this study will provide further evidence on the optimal means to obtain analgesia in patients undergoing gastric bypass surgery.

2.2 References to relevant studies

Transversus abdominis plane (TAP) blocks have been extensively used for intra-operative and post-operative analgesia for various abdominal and gynaecological surgeries. There are many peer-reviewed publications, including systematic reviews and meta-analyses demonstrating improvement in post-operative pain scores and decreased post-operative opioid analgesic consumption in patients undergoing a variety of open surgical procedures [1-3]. Similarly, there is evidence for benefit from TAP blocks in laparoscopic (minimally invasive) surgeries such as laparoscopic cholecystectomies, hernia repairs, and laparoscopic colorectal resections [4-8]. Four studies [9-12] have demonstrated the feasibility of TAP blocks in laparoscopic bariatric surgery, with two of the studies [10, 11] showing a reduction in pain scores and one study [10] showing decreased opioid consumption in patients receiving TAP blocks compared to controls. However, few of published studies have specifically investigated the effectiveness of TAP in patients with morbid obesity undergoing bariatric surgery.

The TAP block is performed by injection of local anesthetic in between the fascial layers of the transversus abdominis and internal oblique muscles of the abdomen, where multiple sensory nerves provide innervation to the abdominal wall [13]. This procedure typically involves injection in the anterior axillary line midway between the sub-costal margin and iliac crest in order to maximize spread of local anesthetic within the transversalis plane. In some situations, especially with midline incisions, a rectus sheath block is also performed. This involves injection of the local anesthetic solution between the anterior and posterior rectus sheath layers on either side of the midline of the abdomen [14]. The Rectus Sheath block has been shown to reduce pain scores post-operatively when utilized on its own, as well as in combination with the TAP block [3, 8]. Pharmacological studies of systemic levels of local anesthetic – most commonly Ropivacaine - concentration following TAP block and Rectus Sheath block confirm their safety in clinical practice [15].

Traditionally, the TAP block and rectus sheath block are completed by an anesthesiologist, either at the beginning or the end of the surgery and utilizing ultrasound guidance to improve accuracy of visualization of the target anatomy and spread of local anesthetic within the appropriate fascial planes. However, in recent years, a new technique has been developed and utilized whereby the surgeon can perform the TAP block under direct visualization during laparoscopic surgery. Multiple studies and technical reports [16-19] describe this laparoscopically-assisted technique. Studies have shown that the laparoscopically-assisted TAP blocks results in similar pain scores and post-operative opioid consumption [20, 21] but shorter block performance time compared to the ultrasound-guided block [20]. In addition, patients receiving a laparoscopically-assisted TAP block had statistically significant reduction in pain scores and opioid consumption compared to controls [19, 22]. A similar laparoscopically-guided technique has been described for rectus sheath block [23].

To date there no published studies of combined laparoscopic-assisted TAP and rectus sheath blocks in the bariatric surgical population.

2. ***Trial Objectives***

The aim of this study is to evaluate the efficacy of a laparoscopically-guided, surgical transversus abdominis plane (TAP) block and rectus sheath block in reducing analgesic consumption while improving functional outcomes in patients undergoing laparoscopic bariatric surgery.

The primary endpoint will be cumulative postoperative opioid analgesic requirements and the secondary endpoints will include post-operative pain scores, change in peak expiratory flow (PEF), and recovery of 6-minute walk test, intra- and post-operative complications, and impact on condition-specific quality of life.

3. *Study Methods*

4.1 Study design

This is a 12-month study. The study compares Tap-Block Ropivacaine versus Tap-Block Normal Saline (placebo control group).

4.2 Study intervention arms

Study subjects will be randomized into two groups:

- Intervention arm – TAP-Block Ropivacaine injection :

  The abdomen will be entered and trocars placed in the usual manner. At the end of surgery, The block will be administered in the anterior abdominal wall. For the TAP block, the standard technique will be followed- at the anterior axillary line midway between the subcostal margin and iliac crest. For the rectus sheath block, a bilateral sub-xiphoid approach will be used. There will be 4 injection sites in total and the size of the needle will be standardized to an 18g spinal needle 10cms. Using laparoscopic visualization, the transversus abdominis muscles were identified lateral to the semilunar line. Ropivacaine to be infiltrated will be divided into 4 equal amounts. The needle will pass through the skin until 2 "pops" are felt, indicating the needle had passed through the 2 fascial layers. When the needle tip was seen just above the peritoneum, it was withdrawn about 3 mm so that the end of the needle was just above the thin transversus abdominis muscle. The needle was now in the plane between the internal oblique and transversus abdominis muscles, allowing the solution to reach the spinal nerves in the plane. Laparoscopic visualization ensured that the needle tip did not penetrate the peritoneum. After injection, a smooth wheal covered by the transversus abdominis muscle could be seen laparoscopically. The procedure is then repeated 2 times in the transversus abdominis plane (20mL each) and 2 times as a Rectus Sheath Block (10mL each) with a total amount of 60 mL.

- Control arm – Normal saline TAP and rectus sheath block Injection: normal saline administered as in intervention arm above

4.3 Patient Population

All adults (over 18 years old) undergoing laparoscopic gastric at the Ottawa Hospital Civic Campus, an Academic Hospital Affiliated with the university of Ottawa

4.4 Inclusion Criteria

- Patients undergoing Roux-en-Y gastric bypass surgery;
- Patients who are able to tolerate general anesthetic and pneumoperitoneum;
- Patients who are able to provide informed consent for the surgery;
- Patients over the age of 18 years;

4.5 Exclusion Criteria

- Patient undergoing planned sleeve gastrectomy (intra-op conversion to sleeve gastrectomy after delivery of Ropivacaine/placebo will be included and analyzed using intention-to-treat approach)
- Patients with an allergy to local anesthetics

- Patients with severe underlying cardiovascular disease (ie: congestive heart failure, conduction abnormalities, and ischemic heart disease)
- Patients with chronic renal disease Stage 3 or greater (Creatinine clearance less than 60mL/min)
- Patients with hepatic dysfunction Child-Pugh Class B or C
- Patients with previous foregut surgery including esophageal, gastric, liver, and pancreas resections
- Patients weighing less than or equal to 100 kilograms as measured in the pre-admission unit
- Patients enrolled in any other study involving tissue biopsy.
- Patients with Chronic Pain and Chronic Opioid use- using Oral Morphine Equivalent of >100mg/day

4.6 Patient recruitment

The Ottawa Hospital Civic Campus pre-admission unit will be used for patient recruitment. Patients will be initially identified as potential candidates by the surgeon, nurse in the clinic then eligibility is verified by the principal investigator.

Consent will be obtained by a research assistant with a medical Background who is independent from the patient's circle of care. The research assistant will also be responsible for ensuring the patients are given accurate information and provided with answers to any questions related to the procedures. If the patient decides to enter the study, then informed consent will be obtained. Individuals responsible for obtaining consent will be trained sufficiently in order to provide patient with accurate unbiased information.

Baseline data will be captured at the clinic at the time of enrollment into trial by Research Assistant. Prior to obtaining informed consent, the following information, much of which would have already been elicited as part of standard practice, will be collected: basic demographic information (i.e. sex, height, weight), existing co-morbidities, past medical and surgical history, medications, allergies and Past history of fibromyalgia, back pain, and arthritis will be documented

4. ***Study outcomes***

4.1 Efficacy outcomes

The primary efficacy endpoint is cumulative postoperative narcotic use administered to subjects during admission and discharge of patients from hospital care measured in their respective units

The secondary efficacy endpoints are:

- Peak expiratory flow score – as measured by the spirometry 60 - 850 liters per minute. Peak expiratory force has not been studied extensively in obese patients. Currently, there is no recommendation on what constitutes a clinically significant change. Recovery to baseline will be sought.
- Post-operative pain score – as measured by the 0-10 Numeric pain rating score (NRS) NRS has been shown to be at least as sensitive as the VAS, [24,25,28-30] and preferred over the commonly used VAS for its relative simplicity and ease of administration and scoring [24,29-31]
- 6-minute walk distance (6MWD) – defined as the distance (m) an individual is able to walk along a flat 30 m walkway over a six-minute period, with breaks as required. Walk testing has been validated in the obese population (27). Clinically significant differences occur when distances of at least 80m occur (27).

4.2 Randomization/Patient allocation/Blinding

Study subjects will be randomized in a 1:1 ratio to intervention and control groups. Randomization will be performed the day prior to surgery to allow the Department of Pharmacy the day prior to surgery to allow adequate time for the trial medications to be prepared. Surgeries booked for Monday will be randomized on Friday.

Once patients are randomized, Pharmacy will prepare the treatment solution Ropivacaine or placebo/Normal Saline) in a standard 60mL injection. The treatment solution will contain the patient's identifier only, and will not indicate to which arm the patient belongs. IV injections will be labeled according to Health Canada regulations. The treatment medication will be delivered to the operating room the day of surgery. The entire operating room staff will be blinded to the treatment allocation. A master copy of treatments received will be kept by the Department of Pharmacy.

4.3 Participants Timeline

	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	***Surgery Consent Visit***	***1 day before surgery***	***Morning of Surgery***	***Intra-operatively***	***Post-Operative day 1***	***Follow-up POD7-10***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Collection of Baseline Data	X					
Allocation		X				
INTERVENTIONS:						
Ropivacaine				X		
Normal Saline				X		
ASSESSMENTS:						
Numeric Pain level	X		X		X	X
Peak Expiratory Flow	X		X		X	X
Analgesic use	X		X	X	X	X

6 minute walk test	X		X		X	X
Quality of life questionnaire	X		X		X	X

4.4 Anaesthetic Protocol

We have standardized the anesthetic protocol for both arms.

- **Premedication:**
  - Acetaminophen 975mg
  - Celecoxib 400mg
- **Anesthetic Induction:**
  - Propofol and Fentanyl or Remifentanil, Rocuronium and Ketamine 20mg
- **Post induction:**
  - Antibiotics, Heparin, Dexamethasone 8mg and Ondansetron 8mg
- **Maintenance**:
  - Air/O2- volatile, Dexmedetomidine 0.4-0.7 mcg/kg/hr, Boluses of Fentanyl as required
  - ketorolac, hydromorphone, and lidocaine will be avoided during surgery
- **Reverse and Extubate:**
  - Neostigmine
  - Glycopyrrolate
- **Postop Orders, at Post Anesthetic Care Unit (PACU)** –
  - Ketorolac
  - Fentanyl: 50mcgIV every 5 minutes max of 250mcg
  - Hydromorphone: 0.2mgIV every 10 minutes max of 2mg

4.5 Un-blinding

Operating room staff will be blinded to the treatment allocation for each patient. If emergency un-blinding is required (at the discretion of the investigator), a request to the on-call Pharmacy Research Technician will be made in order to determine the patient treatment regimen.
If un-blinding occurs for any reason, the event will be recorded in the patients' chart and study file as well as the reasoning behind the un-blinding.

4.6 Patient and Public Involvement

A group five patient advocacy members were invited to meet with study team, presented with study plan and details and input on outcome measures, informed consent wording was obtained. Patients also assessed the study flow and provided feedback on reducing burden on patients. Discussion regarding results dissemination was conducted and results will be shared with study patients who express interest. Patients were not involved in the recruitment of study participant but input was taken on flow of recruitment and applied to study flow.

5. *Statistical Plan*

5.1 Baseline assessment

Baseline characteristics including demographics and relevant medical history will be summarized by standard descriptive summaries (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as sex, ASA scores).

5.2 Efficacy analysis

The primary efficacy endpoint, the use of narcotics will be recorded at baseline and amounts administered will be recorded on the morning of surgery in the same day admit unit, intraoperatively and immediately in recovery room, 0, 4 hours post-operative and then at hours 5 till the period of 24 hours, amount will be recorded in their respective units and the sum is recorded if multiple doses are administered during the any single interval. The cumulative 24-hour morphine equivalents (in mg) will be analyzed with a t-test, comparing treatment arms using the intention-to-treat population, and effect size will be estimated as a mean difference with 95% confidence interval. The intention-to-treat population will include all patients randomized.

For secondary outcomes, the ITT population will be used. A mixed model for repeated measures will be used for continuous quantitative outcomes, comparing treatment arms, to assess treatment effect over the follow-up and to account for ignorable missing data concerns in the secondary outcome measures. Pain scores, will be measured at baseline, on the morning of surgery at the same day admit unit, immediately in recovery room, at 0,and then every 4 hours for a period of 12 hours, then hour 24 and at follow-up seven-ten days post-surgery. PEF will be measured at the same intervals of pain outcome; patients will be encouraged to use the provided PEF in the weeks preceding the surgery, the days after the surgery till their first follow-up. 6MWD will be measured at the baseline, morning of surgery at same day admit unit, on postoperative day one and at clinic follow-up, Patients will be encouraged to practice the 6 minute walk test in the weeks between enrollment, surgery and follow-up.

5.3 Explanatory

Explanatory endpoint

The study treatment period and follow-up is relatively short. As such, explanatory analysis of biomarker, biochemical/ pharmacological parameters over time will not be conducted. Condition quality of life – as measured by the QOR-40 – is the only explanatory efficacy endpoint of interest. The QoR-40 has been validated and was developed specifically for post-operative patients (22).

Explanatory analysis

The explanatory analysis will be based on the treated population. Subjects will be included in the analysis according to the treatment received. QR40 scores will be recorded at baseline, post-operative day 1 and at clinic follow-up. The QR40 will be scored as per questionnaire instructions and will be transformed into summary measures of a 0-100 scale (100 representing the highest quality of life). Raw data and the summary scores will be scored for each patient at each time interval during the recovery period. The analysis will include descriptive and graphical statistics, and comparison of treatment arms will be based on a mixed model for repeated measures, accounting for missing data over follow-up periods.

5.4 Sample Size

Based on data from our previous randomized controlled trial in the same patient population, we expect the mean 24-hr narcotic consumption to be roughly 6 mg of morphine with a standard deviation of 3.79. We consider a 30% reduction in narcotic requirement to be a minimal clinically important difference and we, therefore, need 71 patients per arm in order to obtain 80% power to detect this difference with a t-test, accounting for 5% loss due to follow-up we will be aiming to recruit 75 patients per arm.

5.5 Interim analysis

Interim efficacy analysis is not currently planned. If for any unforeseen reasons, the Date Safety Monitoring Board recommends performing an interim efficacy analysis, a detailed plan will be prepared before the interim efficacy analysis can be conducted. The level for this analysis is set at the 0.0001 level.

6. *Drug Accountability*

Study medication will be stored at the Civic Hospital Pharmacy and will be sourced from the standard Pharmacy supplier. Medication to be used in the study will be demarcated from the clinical supply by Pharmacy technicians and IV bags will be labeled according to Health Canada Division 5 Section C.05.011 regulations. Study drugs will be stored in the research fridge located in a secure, locked location and will be temperature monitored daily. Temperatures min/max are recorded in the daily temperature log and a copy will be stored in the study binder.

A copy of the most current protocol will be submitted to Pharmacy for their records along with the current Health Canada No Objection Letter (NOL). Drug accountability logs detailing the disposition, mixing and/or destruction of study medication will be recorded in the pharmacy accountability logs. The pharmacy will receive the randomization scheme prepared by the OHRI Methods Centre prior to any patients being recruited into the study.

7. *Rescue Medication and Risk Management*

Patients will receive standard cardiorespiratory monitoring (heart rate, blood pressure, EKG, oxygen saturation, end-tidal CO2), temperature, and neuromuscular monitoring throughout the procedure. Gastric bypass typically takes 2-3 hours and therefore patients will have close clinical observation during the expected peak concentration times. In accordance with the American Society of Regional Anesthesia (28) recommendations, patients in the study will be monitored with continuous ECG from the time of administration for the first 24 hours. After emergence from the anesthetic, further specific symptoms of systemic toxicity will be sought. Patients will remain in the Post Anesthetic Care Unit (PACU) for 4-6 hours and then transferred to the monitored step-down unit to allow close cardiovascular and neurological monitoring after the surgery. Patients who develop signs of toxicity will receive prompt and immediate standard ACLS-guided resuscitation and advanced airway management. Depending on their presentation, they may require seizure suppression and or cardio-protective strategies with receive anti-epileptics or 20% lipid emulsion (Intralipid), respectively. These drugs and the ability to provide cardio-respiratory support are available both in the PACU and the step-down unit.

8. *Safety monitoring*

9.1 Serious adverse events

Serious adverse event (SAE) rates will be defined as the fraction of subjects with an SAE.

Anticipated SAEs include the risks of an anesthetic, bleeding, wound infection, bowel injury, unexpected leak, pneumothorax, obstruction and general complications such as a thromboembolic event, pneumonia, cardiac event and stroke. As per current protocol, patients will be contacted by a Nurse Practitioner the day following discharge to ensure they are coping at home. Patients will also be instructed to contact the clinical research team at any time after consenting to join the trial if

they have an event that requires hospitalization or results in persistent or significant disability or incapacity. Ropivacaine is well tolerated and has been studied in the management of other surgical patients. Over 1500 patients were included in these studies; over 600 received Ropivacaine. No clinical toxicities were reported. Serious adverse events are not anticipated in this study. Peak concentrations of Ropivacaine are expected within 30-60 minutes of administration of Ropivacaine. At this time patients will still be in the operating room. Anesthesiologists will be aware of the potential complications of the treatment arm and will monitor appropriately.

9.2 Reporting of safety results

Investigators will report all unanticipated problems (i.e. unexpected, related/possibly related and increases risks of harm) to the Ottawa Health Science Network Research Ethics Board (OHSN-REB) within seven days of the incident or after the investigator becomes aware of the event in accordance to REB SOP OH1003 – Safety Reporting Requirements for Research Involving Human Participants.

The investigators will report all SAEs to the Data Safety Monitoring Board (DSMB) Chair by electronic mail within 7 calendar days after the investigators become aware of the event. A written report will be sent to the DSMB within 15 calendar days.

The investigators will also determine if the SAE is unexpected and related/possibly related to Ropivacaine. An unexpected event for a Ropivacaine is defined as any event not listed in the drug package insert. If the investigators determine that any study-related SAE is unexpected for a Ropivacaine, Health Canada will be notified within 7 calendar days.

9.3 Safety analysis

SAE will be mapped to preferred terms and system organs class using the MedDRA dictionary. The incidence of subjects with a study drug-related SAEs will be summarized by treatment group according to the preferred term and system organ class. Information regarding the occurrence of surgical complications events will be recorded in specific CRFs. SAEs rate will be summarized based on the crude proportion of subjects with one or more SAEs at the time of final analysis. Pearson chi-squared test performed at the 0.05 level, stratified by treatment groups, will be used to compare SAE events rates.

The surgical complication will be classified according to the Clavien-Dindo Classification (www.surgicalcomplication.info/index-2.html). Complication event rates will be summarized based on the crude proportion of subjects will one or more complication events. Pearson chi-squared test performed at the 0.05 level, stratified by treatment groups, will be used to compare events rates based on severity (grade ≥3 versus grade <3).

9. *Data Safety Monitoring Board (DSMB)*

An independent DSMB will be established prior to the randomization of the first patient. The DSMB is an external independent group included at least one expert in trial methodology, anesthesiology and/or bariatric surgery.

The DSMB will perform an ongoing review of safety and efficacy data when the first 40 patients are accrued and after each additional accrual of 40 patients. The responsibilities of the DSMB included:

- To minimize the exposure of patients to unsafe therapy or dose.
- To make recommendations for changes in the study processes, where appropriate
- To advise on the need for dose adjustment for safety issues.
- To endorse study continuation

10. *Premature Withdrawal / Discontinuation Criteria / Stopping Rules*

Patients wishing to withdraw from the study may do so at any point. If they indicate this they will immediately be withdrawn from the study. Withdrawal from the study will not affect patient care, and patients will be made aware of the same during the consent process.

Patients withdrawing from the study will be offered a follow-up appointment with the research assistant to discuss any concerns that arose during their participation in the trial, as well their motivation for withdrawal. This meeting will not be mandatory.

Early withdrawal of participants will be initiated by research staff if:

1. Mechanical complications occur during surgery that are unrelated to the treatment but that may confound post-operative outcomes, e.g. intra-operative hemorrhage, larger spillage of bowel contents, iatrogenic injuries, conversion to laparotomy, etc.
2. Patients are unwilling to follow investigators' instructions

As the DSMB conducts ongoing review of safety data, the investigators may prematurely stop the study in its entirety due to toxicity at the recommendation of DSMB.

11. *GCP Site Monitoring*

Trial monitoring will be performed in order to ensure that the trial-related data is accurate, complete and verifiable from source documents and that patient rights and safety are protected. A qualified study monitor with evidence of training in ICH-GCP and the Division 5 Food and Drug Regulations will be appointed by the Qualified Investigator and will be trained on the Protocol OHRI SOPs, and any specific trial related procedures.

The study monitor will address deficiencies noted in the monitoring visit(s) to the appropriate study team member in order to implement corrective actions or to recommend follow-up procedures. All observations noted during the monitoring visit will appear in the monitoring report and will be submitted to the research team for their review as well as to the OHRI Internal Monitor.
The study Monitoring Plan details the activities to be performed by the monitor and the research team prior to, during and following a monitoring visit.

12. ***Details of the Team***

The study team will be comprised of the principal investigator (PI), co-investigators and research coordinator, Research Assistant and Data Entry Clerk.

The PI, Dr.Mamazza is a General Surgeon and extensive clinical experience in the area of minimally invasive surgery (MIS), gastrointestinal surgery (bariatric, colorectal and foregut surgery) and expertise in the conduct of surgical research and methodology. Dr. Mamazza has mentored over 80 postgraduate surgical trainees, including training 24 clinical and research fellows in advanced MIS techniques. He has dedicated his career to the development and promotion of minimally invasive surgery as it pertains to body cavity surgery with a particular interest bariatric, foregut and colorectal cancer surgery.

The PI will be responsible for ensuring ethical principal and rigors study methodology. He will have the final approval of all reports and scientific publications emanating from the study.

Co- investigators, Dr. Naveen Eipe is the Clinical Anesthesia Lead of Bariatric Surgery Program, the Vice president of Education of the International Society for Perioperative Care of the Obese Patient (ISPCOP) and has extensive experience in pain management in Bariatric population and was involved in multiple studies aiming to improve pain management in the Bariatric population in addition to Doctors Caolan Walsh, Amer Jarrar and Adele Budiansky will provide additional expertise in bariatric surgery, anesthesia and research. The team will have the overall responsibility for the design, execution, and analysis of the trial and will meet every month to discuss all pertinent issues.

Protocol, Forms review and RCT feedback was provided by our patient advocacy group, Marc Tessier, Sharon Ellis, Suzanne Dugas, Suzanne Lavigne and Nick Seguin and we thank them for their valuable input, contribution and time.

13. *Publication*

The study results, regardless of the outcome, will be reported in a manuscript submitted for a medical/surgical journal.

The uniform requirements for manuscripts submitted to medical journals (based on the Vancouver statement) will apply. Authorship will be based only on substantial contribution to:

- Concept and design, or analysis and interpretation of data.
- Drafting of the article or revising it critically for important intellectual content.
- On final approval of the version to be published.

All these conditions must be met. Participation solely in the acquisition of funding or collection of data does not justify authorship.

There will be an acknowledgement of all contributors (referring surgeons, data managers, research nurses).

14. *References*

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1,2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,11
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7,9,10
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1,2
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods:			

Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5,6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8,9

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5,6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5,6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5,6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5,6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	12

		collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7,8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7,8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7,8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9,10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9,10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9,10
Ethics and			

dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA (Ethics application)
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	External Document
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	External Document
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Notes:

- 25: NA (Ethics application)
- 28: External Document
- 29: External Document The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 25. July 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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2. Surname (Last Name): Budiansky
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Corresponding Author's Name: Amer Jarrar

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4. Intellectual Property.

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Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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Royalties: Funds are coming in to you or your institution due to your patent

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Section 1. Identifying Information

1. Given Name (First Name): Caolan
2. Surname (Last Name): Walsh
3. Date: 02-August-2018

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Amer Jarrar

5. Manuscript Title
Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Laparoscopic Transversus Abdominis Plane Block in Gastric Bypass Surgery

6. Manuscript Identifying Number (if you know it)

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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2. Surname (Last Name): Jarrar
3. Date: 02-August-2018

4. Are you the corresponding author? ☑ Yes ☐ No

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2. Surname (Last Name): Eipe
3. Date: 02-August-2018

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1,2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,11

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7,9,10
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1,2
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5,6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8,9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for	5,6

		stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5,6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5,6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5,6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the	12

		protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7,8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7,8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7,8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9,10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9,10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9,10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA (Ethics application)

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	External Document
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	External Document
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Notes:

- 25: NA (Ethics application)

- 28: External Document
- 29: External Document The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 25. July 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Laparoscopic Transversus Abdominis Plane Block in Gastric Bypass Surgery, a Study Protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025818.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Apr-2020
Complete List of Authors:	Jarrar, Amer; The Ottawa Hospital, Surgery Budiansky, Adele; The Ottawa Hospital, Anesthesia Eipe, Naveen; The Ottawa Hospital, Anesthesia Walsh, Caolan; The Ottawa Hospital, Surgery Kolozsvari, Nicole; The Ottawa Hospital, General Surgery Neville, Amy; The Ottawa Hospital Civic Campus, Surgery Mamazza, Joseph; The Ottawa Hospital Civic Campus, Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Anaesthesia, Evidence based practice, Patient-centred medicine
Keywords:	Morbid Obesity, Pain management < ANAESTHETICS, Gastric Bypass, TAP Block, Opioid Sparring, ERAS

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Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Laparoscopic Transversus Abdominis Plane Block in Gastric Bypass Surgery, a Study Protocol.

LapTAP Trial

Co-Investigators:

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Current Version: Version 5- March 10,2020

Previous Versions: -Version 4- July 20 2019

-Version 3- November 20 2018

-Version 2- October 1, 2017

-Version 1 - September 27, 2017

Sponsor: Ottawa Hospital Research Institute

Civic Box 675, 725 Parkdale Avenue,

Ottawa, Ontario K1Y 4E9

613-798-5555 ext. 16719

Fax: 613-761-4311

ClinicalTrials.gov Identifier: NCT03367728

OHSN-REB Identifier: 20170749-01H

Universal Trial Number (UTN): U1111-1206-9983

Word Count: 4665 words.

ABSTRACT

Introduction: Evaluating the efficacy of a laparoscopically-guided, surgical transversus abdominis plane (TAP) and rectus sheath (RS) block in reducing analgesic consumption while improving functional outcomes in patients undergoing laparoscopic bariatric surgery.

Methods: 150 morbidly obese patients undergoing elective laparoscopic Roux-En-Y gastric bypass (LRYGB) for obesity will be recruited to this double-blinded, placebo-controlled Randomized Control Trial from a Bariatric Centre of Excellence over a period of six months. Patients will be electronically randomised on a 1:1 basis to either an intervention or placebo group. Those on the intervention arm will receive a total of 60 mL 0.25% ropivacaine, divided into four injections: two for TAP and two for RS block under laparoscopic visualization. The placebo arm will receive normal saline in the same manner. A standardized surgical and anaesthetic protocol will be followed, with care in adherence to the Enhanced Recovery after Bariatric Surgery (ERABS) guidelines.

Analysis: Demographic information and relevant medical history will be collected from the 150 patients enrolled in the study. Our primary efficacy endpoint is cumulative postoperative narcotic use. Secondary outcomes are peak expiratory flow (PEF), Post-operative pain score and the 6-minute walk test. Quality of recovery will be assessed using a validated questionnaire (QoR-40). Statistical analysis will be conducted to assess differences within and between the two groups. The repeated measures will be analysed by a mixed modelling approach and results reported through publication.

Ethics and dissemination: Ethics approval was obtained (20170749-01H) through our institutional research ethics board (Ottawa Health Science Network Research Ethics Board) and the study results, regardless of the outcome, will be reported in a manuscript submitted for a medical/surgical journal.

Keywords: Bariatrics, Trans-abdominis Plane block, TAP-Block, gastric bypass, Enhanced Recovery, ERAS.

ARTICLE SUMMARY

Strength and Limitations

Strength:

- RCT conducted at a Bariatric centre of Excellence.
- A large Number of Patients.
- Standardized Surgical and Anaesthetic technique.
- First RCT to assess TAP and Rectus Sheath Blocks in Bariatric Patients.
- A study limitation maybe the block timing administration at the end of the case instead of case start as suggested in some of the new evidence.

INTRODUCTION

Background

Management of post-operative pain remains a significant challenge and an area of continued research. [1–3] Effective pain control, apart from providing general patient comfort, is critical for a variety of clinical reasons. It leads to early ambulation and improved respiratory function, which significantly reduces the risk of post-operative complications such as pulmonary embolus or pneumonia, as well as early discharge. [1]

Post-operative pain management was typically opioid-based; however, post-operative opioid use may be associated with increased risk of respiratory depression and sedation. It is therefore desirable to implement opioid-sparing multimodal analgesia to achieve satisfactory pain control while reducing post-operative opioid requirements and their side-effects. [4,5]

Rational pain management is a particularly pertinent issue in patients with morbid obesity (M.O.). [6] The pathophysiology of obesity, the high prevalence of obstructive sleep apnea, and high susceptibility to respiratory depression amongst patients with M.O. make safe analgesic management especially difficult. These individuals are at high risk of postoperative adverse respiratory events, nosocomial infections, cardiovascular complications, and pulmonary emboli (the second leading cause of death in the bariatric surgery population). [6,7]

Given the increasing number of patients with morbid obesity presenting for elective weight loss surgery, it is crucial to understand and optimise the analgesic requirements of this patient population.[8] However, there are limited evidence-based recommendations and no ideal analgesic regimen exists for patients with M.O. Current recommendations include use of step-wise severity-based opioid-sparing multimodal analgesia. It is possible that including local anaesthetic blocks will further reduce pain, opioid analgesic consumption and side-effects from pain management (sedation, confusion, nausea & vomiting, etc.) at-risk patient population. [6,7,9]

The aim of this study is to evaluate the efficacy of a laparoscopically-guided, surgical transversus abdominis plane (TAP) block and rectus sheath block in reducing post-operative opioid consumption and improving outcomes in patients undergoing laparoscopic gastric bypass surgery. The results of this study will provide further evidence on the optimal means

to obtain analgesia in patients undergoing gastric bypass surgery.

References to relevant studies

Transversus abdominis plane (TAP) blocks have been extensively used for intra-operative and post-operative analgesia for various abdominal and gynaecological surgeries. [10–12] There are many peer-reviewed publications, including systematic reviews and meta-analyses demonstrating improvement in A large pain scores and decreased post-operative opioid analgesic consumption in patients undergoing a variety of open surgical procedures.[13–15] Similarly, there is evidence for benefit from TAP blocks in laparoscopic (minimally invasive) surgeries such as laparoscopic cholecystectomies, hernia repairs, and laparoscopic colorectal resections.[16–20] Four studies have [21–24]demonstrated the feasibility of TAP blocks in laparoscopic bariatric surgery, with two of the studies [22,23] showing a reduction in pain scores and one study [22] showing decreased opioid consumption in patients receiving TAP blocks compared to controls. However, few of published studies have specifically investigated the effectiveness of TAP in patients with morbid obesity undergoing bariatric surgery.

The TAP block is performed by injection of local anaesthetic in between the fascial layers of the transversus abdominis and internal oblique muscles of the abdomen, where multiple sensory nerves provide innervation to the abdominal wall.[10] This procedure typically involves injection in the anterior axillary line midway between the sub-costal margin and iliac crest in order to maximize spread of local anaesthetic within the transversalis plane. In some situations, especially with midline incisions, a rectus sheath block is also performed. This involves injection of the local anaesthetic solution between the anterior and posterior rectus sheath layers on either side of the midline of the abdomen. [25]The Rectus Sheath block has been shown to reduce pain scores post-operatively when utilized on its own, as well as in combination with the TAP block.[15,20] Pharmacological studies of systemic levels of local anaesthetic – most commonly Ropivacaine - concentration following TAP block and Rectus Sheath block confirm their safety in clinical practice. [26]

Traditionally, the TAP block and rectus sheath block are completed by an anaesthesiologist, either at the beginning or the end of the surgery and utilizing ultrasound guidance to improve accuracy of visualization of the target anatomy and spread of local anaesthetic within the appropriate fascial planes. However, in recent years, a new technique has been developed and

utilized whereby the surgeon can perform the TAP block under direct visualization during laparoscopic surgery. Multiple studies and technical reports [27–30] describe this laparoscopically-assisted technique. Studies have shown that the laparoscopically-assisted TAP blocks result in similar pain scores and post-operative opioid consumption [31,32] but shorter block performance time compared to the ultrasound-guided block.[31] In addition, patients receiving a laparoscopically-assisted TAP block had statistically significant reduction in pain scores and opioid consumption compared to controls.[30,33] A similar laparoscopically-guided technique has been described for rectus sheath block.[34]

To date there are no published studies of combined laparoscopic-assisted TAP and rectus sheath blocks in the bariatric surgical population.

METHODS AND ANALYSIS

Trial objectives

The aim of this study is to evaluate the efficacy of a laparoscopically-guided, surgical transversus abdominis plane (TAP) block and rectus sheath block in reducing analgesic consumption while improving functional outcomes in patients undergoing laparoscopic bariatric surgery.

The primary endpoint will be cumulative postoperative opioid analgesic requirements and the secondary endpoints will include post-operative pain scores, change in peak expiratory flow (PEF), and recovery of 6-minute walk test, intra- and post-operative complications, and impact on condition-specific quality of life.

Study design

Randomized placebo controlled trial comparing Tap-Block Ropivacaine versus Tap-Block Normal Saline (placebo control group).

Study intervention arms

Study subjects will be randomized into two groups:

- Intervention arm – TAP-Block Ropivacaine injection:

The abdomen will be entered and trocars placed in the usual manner. At the end of surgery, the block will be administered in the anterior abdominal wall. For the TAP block, the standard technique will be followed- at the anterior axillary line midway between the subcostal margin and iliac crest. For the rectus sheath block, a bilateral sub-xiphoid approach will be used. There will be 4 injection sites in total and the size of the needle will be standardized to an 18g spinal needle 10cms. Using laparoscopic visualization, the transversus abdominis muscles were identified lateral to the semilunar line. Ropivacaine to be infiltrated will be divided into 4 equal amounts. The needle will pass through the skin until 2 "pops" are felt, indicating the needle had passed through the 2 fascial layers. When the needle tip was seen just above the peritoneum, it was withdrawn about 3 mm so that the end of the needle was just above the thin transversus abdominis muscle. The needle was now in the plane between the internal oblique and transversus abdominis muscles, allowing the solution to reach the spinal nerves in the plane. Laparoscopic visualization ensured that the needle tip did not penetrate the peritoneum. After injection, a smooth wheal covered by the transversus abdominis muscle could be seen laparoscopically. The procedure is then repeated 2 times in the transversus abdominis plane (20mL each) and 2 times as a Rectus Sheath Block (10mL each) with a total amount of 60 mL of 0.25% Ropivacaine.

- Control arm – Normal saline TAP and rectus sheath block Injection: normal saline administered as in intervention arm above

Patient population

All adults (over 18 years old) undergoing laparoscopic gastric at the Ottawa Hospital Civic Campus**,** an Academic Hospital Affiliated with the university of Ottawa

Inclusion Criteria

- Patients undergoing Roux-en-Y gastric bypass surgery;
- Patients who are able to tolerate general anaesthetic and pneumoperitoneum;
- Patients who are able to provide informed consent for the surgery;
- Patients over the age of 18 years;

Exclusion criteria

- Patient undergoing planned sleeve gastrectomy (intra-op conversion to sleeve gastrectomy after delivery of Ropivacaine/placebo will be included and analysed using intention-to-treat approach)
- Patients with an allergy to local anaesthetics
- Patients with severe underlying cardiovascular disease (i.e.: congestive heart failure, conduction abnormalities, and ischemic heart disease)
- Patients with chronic renal disease Stage 3 or greater (Creatinine clearance less than 60mL/min)
- Patients with hepatic dysfunction Child-Pugh Class B or C
- Patients with previous foregut surgery including oesophageal, gastric, liver, and pancreas resections
- Patients weighing less than or equal to 100 kilograms as measured in the pre-admission unit
- Patients enrolled in any other study involving tissue biopsy.
- Patients with chronic pain and chronic opioid use- using oral morphine equivalent of >100mg/day

Patient recruitment

The Ottawa Hospital Civic Campus pre-admission unit will be used for patient recruitment. Patients will be initially identified as potential candidates by the surgeon or nurse in the clinic then eligibility is verified by the principal investigator.

Written consent will be obtained by a research assistant with a medical background who is independent from the patient's circle of care. The research assistant will also be responsible for ensuring the patients are given accurate information and provided with answers to any questions related to the procedures. If the patient decides to enter the study, then informed consent will be obtained. Individuals responsible for obtaining consent will be trained

sufficiently in order to provide patient with accurate unbiased information.

Baseline data will be captured at the clinic at the time of enrolment into trial by the research assistant. Prior to obtaining informed consent, the following information, much of which would have already been elicited as part of standard practice, will be collected: basic demographic information (i.e. sex, height, weight), existing co-morbidities, past medical and surgical history, medications, allergies and past history of fibromyalgia, back pain, and arthritis will be documented.

Study outcomes

Efficacy outcomes

The primary efficacy endpoint is cumulative postoperative narcotic use administered to subjects during admission (limited to 24 hours post-operation) in their respective units.

The secondary efficacy endpoints are:

- Peak expiratory flow score – as measured by the spirometry 60 - 850 litres per minute. Peak expiratory force has not been studied extensively in obese patients. Currently, there is no recommendation on what constitutes a clinically significant change. Recovery to baseline will be sought.

- Post-operative pain score – as measured by the 0-10 Numeric rating Score (NRS) NRS has been shown to be at least as sensitive as the VAS [35–39] and preferred over the commonly used VAS for its relative simplicity and ease of administration and scoring. [35,38–40]

- 6-minute walk distance (6MWD) – defined as the distance (m) an individual is able to walk along a flat 30 m walkway over a six-minute period, with breaks as required. Walk testing has been validated in the obese population.[41] An improved walking distance of at least 80 m is required to be 95% certain of a true change in the individual making the mentioned change the accepted clinically significant difference required.[41]

Explanatory outcome

The study treatment period and follow-up are relatively short. As such, explanatory analysis of biomarker, biochemical/ pharmacological parameters over time will not be conducted. Condition quality of life – as measured by the QOR-40 – is the only explanatory efficacy endpoint of interest. The QoR-40 has been validated and was developed specifically for post-operative patients.

Randomization/Patient allocation/Blinding

Study subjects will be randomized in a 1:1 ratio to intervention and control groups. Randomization will be performed the day prior to surgery allowing the Department of Pharmacy adequate time for the trial medications to be prepared. Surgeries booked for Monday will be randomized on Friday.

Once patients are randomized, Pharmacy will prepare the treatment solution Ropivacaine or placebo/Normal Saline) in a standard 60mL injection. The treatment solution will contain the patient's identifier only, and will not indicate to which arm the patient belongs. IV injections will be labelled according to Health Canada regulations. The treatment medication will be delivered to the operating room the day of surgery. The entire operating room staff will be blinded to the treatment allocation. A master copy of treatments received will be kept by the Department of Pharmacy.

Participants Timeline

Participants will be screened for enrolment eligibility during routine surgery consent visit. If enrolled, the data will be collected pre- and post-operative as detailed in Tab. 1.

	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	***Surgery Consent Visit***	***1 day before surgery***	***Morning of Surgery***	***Intra-operatively***	***Post-Operative day 1***	***Follow-up POD7-10***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					

Collection of Baseline Data	X					
Allocation		X				
INTERVENTIONS:						
Ropivacaine				X		
Normal Saline				X		
ASSESSMENTS:						
Numeric rating Scale	X		X		X	X
Peak Expiratory Flow	X		X		X	X
Analgesic use	X		X	X	X	X
6-minute walk test	X		X		X	X
Quality of life questionnaire	X		X		X	X

Tab. 1. Participant timeline.

Anaesthetic Protocol

We have standardised the anaesthetic protocol for both arms.

- Premedication:
  - acetaminophen 975mg
  - celecoxib 400mg
- Anaesthetic Induction:
  - propofol and fentanyl or remifentanil, rocuronium and ketamine 20mg
- Post induction:
  - antibiotics, heparin, dexamethasone 8mg and ondansetron 8mg

- Maintenance:
    - Air/O2- volatile, dexmedetomidine 0.4-0.7 mcg/kg/hr, boluses of fentanyl as required
    - ketorolac, hydromorphone, and lidocaine will be avoided during surgery
- Reverse and Extubate:
    - neostigmine
    - glycopyrrolate
- Postop Orders, at Post Anaesthetic Care Unit (PACU) –
    - ketorolac
    - fentanyl: 50mcgIV every 5 minutes max of 250mcg
    - hydromorphone: 0.2mgIV every 10 minutes max of 2mg

Un-blinding

Operating room staff will be blinded to the treatment allocation for each patient. If emergency un-blinding is required (at the discretion of the investigator), a request to the on-call Pharmacy Research Technician will be made in order to determine the patient treatment regimen.

If un-blinding occurs for any reason, the event will be recorded in the patients' chart and study file as well as the reasoning behind the un-blinding.

Patient and Public Involvement

A group of five patient advocacy members were invited to meet with study team, presented with study plan and details and input on outcome measures, informed consent wording was obtained. Patients also assessed the study flow and provided feedback on reducing burden on

patients. Discussion regarding results dissemination was conducted and results will be shared with study patients who express interest. Patients were not involved in the recruitment of study participant but input was taken on flow of recruitment and applied to study flow.

Statistical Plan

Baseline assessment

Baseline characteristics including demographics and relevant medical history will be summarized by standard descriptive summaries (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as sex, ASA scores).

Efficacy analysis

The primary efficacy endpoint, the use of narcotics will be recorded at baseline, throughout the patient's stay at the hospital at set intervals up to a maximum of 24 hours postoperatively. The cumulative 24-hour morphine equivalents (in mg) will be analysed with a t-test, comparing treatment arms using the intention-to-treat population, and effect size will be estimated as a mean difference with 95% confidence interval. The intention-to-treat population will include all patients randomized.

For secondary outcomes, the ITT population will be used. A mixed model for repeated measures will be used for continuous quantitative outcomes, comparing treatment arms, to assess treatment effect over the follow-up and to account for ignorable missing data in the secondary outcome measures. Pain scores will be measured at baseline, on the morning of surgery at the same day admit unit, immediately in the recovery room, at 0, and then every 4 hours for 12 hours, then hour 24 and at follow-up seven-ten days post-surgery. PEF will be measured at the same intervals of pain outcome; patients will be encouraged to use the provided PEF in the weeks preceding the surgery, and on the days after the surgery till their first follow-up. 6MWD will be measured at the baseline, morning of surgery at same day

admit unit, on postoperative day one and at clinic follow-up, Patients will be encouraged to practice the 6-minute walk test in the weeks between enrolment, surgery and follow-up.

Explanatory analysis

The explanatory analysis will be based on the treated population. Subjects will be included in the analysis according to the treatment received. QR40 scores will be recorded at baseline, post-operative day 1 and at clinic follow-up. The QR40 will be scored as per questionnaire instructions and will be transformed into summary measures of a 0-100 scale (100 representing the highest quality of life). Raw data and the summary scores will be scored for each patient at each time interval during the recovery period. The analysis will include descriptive and graphical statistics, and comparison of treatment arms will be based on a mixed model for repeated measures, accounting for missing data over follow-up periods.

Sample size

Based on data from our previous randomized controlled trial in the same patient population, we expect the mean 24-hr narcotic consumption (Orally, intravenous or subcutaneously) to be roughly 6 mg of morphine equivalent with a standard deviation of 3.79. We consider a 30% reduction in narcotic requirement to be a minimal clinically important difference and we, therefore, need 71 patients per arm in order to obtain 80% power to detect this difference with a t-test, accounting for 5% loss due to follow-up we will be aiming to recruit 75 patients per arm.

Interim analysis

Interim efficacy analysis is not currently planned. If for any unforeseen reasons, the Date Safety Monitoring Board recommends performing an interim efficacy analysis, a detailed plan will be prepared before the interim efficacy analysis can be conducted. The level for this analysis is set at the 0.0001 level.

Data Normality

Prior to conducting the above planned analysis, data will be tested for normality, if data is found not to be normally distributed; non-parametric methods will be used for analysis.

ETHICS AND DISSEMINATION

Drug Accountability

Study medication will be stored at the Civic Hospital Pharmacy and will be sourced from the standard Pharmacy supplier. Medication to be used in the study will be demarcated from the clinical supply by Pharmacy technicians and IV bags will be labelled according to Health Canada Division 5 Section C.05.011 regulations. Study drugs will be stored in the research fridge located in a secure, locked location and will be temperature monitored daily. Temperatures min/max are recorded in the daily temperature log and a copy will be stored in the study binder.

A copy of the most current protocol will be submitted to Pharmacy for their records along with the current Health Canada No Objection Letter (NOL). Drug accountability logs detailing the disposition, mixing and/or destruction of study medication will be recorded in the pharmacy accountability logs. The pharmacy will receive the randomisation scheme prepared by the OHRI Methods Centre before any patients being recruited into the study.

Rescue Medication and Risk Management

Patients will receive standard cardiorespiratory monitoring (heart rate, blood pressure, EKG, oxygen saturation, end-tidal CO2), temperature, and neuromuscular monitoring throughout the procedure. Gastric bypass typically takes 2-3 hours and therefore patients will have close clinical observation during the expected peak concentration times. In accordance with the American Society of Regional Anaesthesia (recommendations, patients in the study will be monitored with continuous ECG from the time of administration for the first 24 hours. After emergence from the anaesthetic, further specific symptoms of systemic toxicity will be sought. Patients will remain in the Post Anaesthetic Care Unit (PACU) for 4-6 hours and then transferred to the monitored step-down unit to allow close cardiovascular and neurological monitoring after the surgery. Patients who develop signs of toxicity will receive prompt and immediate standard ACLS-guided resuscitation and advanced airway management. Depending on their presentation, they may require seizure suppression and or cardio-protective strategies with anti-epileptics or 20% lipid emulsion (Intralipid),

respectively. These drugs and the ability to provide cardio-respiratory support are available both in the PACU and the step-down unit.

Safety monitoring

Serious adverse events

Serious adverse event (SAE) rates will be defined as the fraction of subjects with an SAE.

Anticipated SAEs include the risks of an anaesthetic, bleeding, wound infection, bowel injury, unexpected leak, pneumothorax, obstruction and general complications such as a thromboembolic event, pneumonia, cardiac event and stroke. As per current protocol, patients will be contacted by a Nurse Practitioner the day following discharge to ensure they are coping at home. Patients will also be instructed to contact the clinical research team at any time after consenting to join the trial if they have an event that requires hospitalization or results in persistent or significant disability or incapacity. Ropivacaine is well tolerated and has been studied in the management of other surgical patients. Over 1500 patients were included in these studies; over 600 received Ropivacaine. No clinical toxicities were reported. Serious adverse events are not anticipated in this study. Peak concentrations of Ropivacaine are expected within 30-60 minutes of administration of Ropivacaine. At this time patients will still be in the operating room. Anaesthesiologists will be aware of the potential complications of the treatment arm and will monitor appropriately.

Reporting of safety results

Investigators will report all unanticipated problems (i.e. unexpected, related/possibly related and increases risks of harm) to the Ottawa Health Science Network Research Ethics Board (OHSN-REB) within seven days of the incident or after the investigator becomes aware of the event in accordance to REB SOP OH1003 – Safety Reporting Requirements for Research Involving Human Participants.

The investigators will report all SAEs to the Data Safety Monitoring Board (DSMB) Chair by electronic mail within 7 calendar days after the investigators become aware of the event. A written report will be sent to the DSMB within 15 calendar days.

The investigators will also determine if the SAE is unexpected and related/possibly related to Ropivacaine. An unexpected event for a Ropivacaine is defined as any event not listed in the drug package insert. If the investigators determine that any study-related SAE is unexpected for a Ropivacaine, Health Canada will be notified within 7 calendar days.

Safety analysis

SAE will be mapped to preferred terms and system organs class using the MedDRA dictionary. The incidence of subjects with a study drug-related SAEs will be summarized by treatment group according to the preferred term and system organ class. Information regarding the occurrence of surgical complications events will be recorded in specific CRFs. SAEs rate will be summarized based on the crude proportion of subjects with one or more SAEs at the time of final analysis. Pearson chi-squared test performed at the 0.05 level, stratified by treatment groups, will be used to compare SAE events rates.

The surgical complication will be classified according to the Clavien-Dindo Classification[42] Complication event rates will be summarized based on the crude proportion of subjects will one or more complication events. Pearson chi-squared test performed at the 0.05 level, stratified by treatment groups, will be used to compare events rates based on severity (grade ≥3 versus grade <3).

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established prior to the randomization of the first patient. The DSMB is an external independent group included at least one expert in trial methodology, anaesthesiology and/or bariatric surgery.

The DSMB will perform an ongoing review of safety and efficacy data when the first 40 patients are accrued and after each additional accrual of 40 patients. The responsibilities of the DSMB included:

- To minimize the exposure of patients to unsafe therapy or dose.
- To make recommendations for changes in the study processes, where appropriate
- To advise on the need for dose adjustment for safety issues.

- To endorse study continuation

Premature Withdrawal / Discontinuation Criteria / Stopping Rules

Patients wishing to withdraw from the study may do so at any point. If they indicate this they will immediately be withdrawn from the study. Withdrawal from the study will not affect patient care, and patients will be made aware of the same during the consent process.

Patients withdrawing from the study will be offered a follow-up appointment with the research assistant to discuss any concerns that arose during their participation in the trial, as well their motivation for withdrawal. This meeting will not be mandatory.

Early withdrawal of participants will be initiated by research staff if:

1. Mechanical complications occur during surgery that are unrelated to the treatment but that may confound post-operative outcomes, e.g. intra-operative haemorrhage, larger spillage of bowel contents, iatrogenic injuries, conversion to laparotomy, etc.

2. Patients are unwilling to follow investigators' instructions

As the DSMB conducts ongoing review of safety data, the investigators may prematurely stop the study in its entirety due to toxicity at the recommendation of DSMB.

GCP Site Monitoring

Trial monitoring will be performed in order to ensure that the trial-related data is accurate, complete and verifiable from source documents and that patient rights and safety are protected. A qualified study monitors with evidence of training in ICH-GCP and the Division 5 Food and Drug Regulations will be appointed by the Qualified Investigator and will be trained on the Protocol OHRI SOPs, and any specific trial related procedures.

The study monitor will address deficiencies noted in the monitoring visit(s) to the appropriate study team member in order to implement corrective actions or to recommend follow-up procedures. All observations noted during the monitoring visit will appear in the monitoring report and will be submitted to the research team for their review as well as to the OHRI Internal Monitor.

The study Monitoring Plan details the activities to be performed by the monitor and the research team prior to, during and following a monitoring visit.

Details of the Team

The study team will be comprised of the principal investigator (PI), co-investigators and research coordinator, Research Assistant and Data Entry Clerk.

The PI, Dr.Mamazza is a General Surgeon with extensive clinical experience in the area of minimally invasive surgery (MIS), gastrointestinal surgery (bariatric, colorectal and foregut surgery) and expertise in the conduct of surgical research and methodology and was the principal investigator for multiple randomized controlled trials at our institution. Dr. Mamazza has mentored over 80 postgraduate surgical trainees, including training 24 clinical and research fellows in advanced MIS techniques. He has dedicated his career to the development and promotion of minimally invasive surgery as it pertains to body cavity surgery with a particular interest in bariatric, foregut and colorectal cancer surgery and was the chief of division of general surgery.

The PI will be responsible for ensuring ethical principal and rigors study methodology. He will have the final approval of all reports and scientific publications emanating from the study.

Co- investigators, Dr. Naveen Eipe is the Clinical Anaesthesia Lead of Bariatric Surgery Program, the Vice president of Education of the International Society for Perioperative Care of the Obese Patient (ISPCOP) and has extensive experience in pain management in the Bariatric population and was involved in multiple studies aiming to improve pain management in the Bariatric population in addition to Doctors Caolan Walsh, Nicole Kolozsvari, Amy Neville, and Adele Budiansky will provide additional expertise in bariatric surgery, anaesthesia and research. The team will have the overall responsibility for the design, execution, and analysis of the trial and will meet every month to discuss all pertinent issues; Dr. Amer Jarrar is leading the design and conduct of the trial. Protocol, Forms review and RCT feedback was provided by our patient advocacy group, Marc T., Sharon E., Suzanne D., Suzanne L. and Nick S. and we thank them for their valuable input, contribution and time.

Protocol Version

The latest edition of the study protocol was approved by The Ottawa Health Science Network Research Ethics Board (OHSN-REB) on March 10th 2020. The SPIRIT reporting guidelines were used during preparation of this protocol.(Supplementary file)[43]

Amendments to Protocol

All Amendments to Protocol were reviewed and approved by OHSN-REB, the participating providers and co-investigators informed of any updates on the study recruitment timeline and any major protocol changes during the enrolment period through regular meetings. All significant protocol changes will be noted on ClinicalTrials.gov.

Confidentiality

Special efforts are made to protect the privacy of subjects. All personal identifying information (PII), such as names, addresses, phone numbers and email addresses are kept in a secure database, all information collected will be identified with a unique study numbers, a master list providing the link between PII and study numbers is stored securely in adherence to OHSN-REB regulations.

All paper and electronic information will be surely shredded in compliance with the law after the storage period required by law.

Dissemination

The study results, regardless of the outcome, will be reported in a manuscript submitted for a medical/surgical journal.

The uniform requirements for manuscripts submitted to medical journals (based on the Vancouver statement) will apply. Authorship will be based only on substantial contribution to:

Concept and design, or analysis and interpretation of data.

Drafting of the article or revising it critically for important intellectual content.

On final approval of the version to be published.

All these conditions must be met. Participation solely in the acquisition of funding or collection of data does not justify authorship.

There will be an acknowledgement of all contributors (referring surgeons, data managers, research nurses).

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AUTHORS CONTRIBUTION:

- **Dr.Amer Jarrar:** The corresponding author and lead the design and conduct of the trial, has contributed the most to this protocol, approved the final version of this document and agrees to be accountable for all aspects of this work's accuracy and integrity.
- **Dr. Adele Budiansky:** Provided substantial contribution to the design of the trial and drafting of the protocol, including the back background and anesthesia component, approved the final version of this document and agreed to be accountable for all aspects of this work's accuracy and integrity.
- **Dr. Naveen Eipe:** Provided substantial contribution to the design of the trial, providing substantial feedback on the anesthesia component of this trial as the Clinical Anaesthesia Lead of Bariatric Surgery Program, He contributed to revising and drafting of this document for intellectual content, approved the final version of this document and agrees to be accountable for all aspects of this work's accuracy and integrity.
- **Dr. Caolan Walsh:** Provided substantial contribution to the design of the trial and drafting of the protocol, revised the surgical components of this trial, approved the final version of this document and agrees to be accountable for all aspects of this work, approved the final version of this document and agreed to be accountable for all aspects of this work's accuracy and integrity.
- **Dr. Nicole Kolozsvari:** Provided substantial contribution to the design of the trial and drafting of the protocol, revised the surgical components of this trial, approved the final version of this document and agrees to be accountable for all aspects of this work, approved the final version of this document and agreed to be accountable for all aspects of this work's accuracy and integrity.
- **Dr. Amy Neville:** Provided substantial contribution to the design of the trial and drafting of the protocol, revised the surgical components of this trial, approved the final version of this document and agrees to be accountable for all aspects of this work, approved the final version of this document and agreed to be accountable for all aspects of this work's accuracy and integrity.
- **Dr. Joseph Mamazza:** The Principal Investigator for this trial, responsible for ensuring ethical principal and rigors study methodology. He will have the final approval of all reports and scientific publications emanating from the study, As a leading surgeon in the field he was able to provide substantial input to design of the trial, and assisted and supervised the document for important intellectual content, has approved this version and agreed to be accountable for all aspects of this work's accuracy and integrity.

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Reporting checklist for protocol of a clinical trial. Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	28
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,20,28
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2,
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1,17,21
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9,10,20
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each	5,6

	intervention		
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5,6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7,8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8,9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	16,17,18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	18
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event),	10,11

		method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11,12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8,9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking):	#17b	If blinded, circumstances under which unblinding	13

emergency unblinding		is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11,12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9,
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12,14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15,18
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15,18
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting	18

		structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9,10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	28

	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21
	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	28
	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
	Appendices			
	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	External Document
	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a