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A Pilot Study to Assess the Feasibility of a Future Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Intra-Peritoneal Ropivacaine in Gastric Bypass Surgery: the INOPAIN (INtrapertoneal rOPivAcaine use IN bariatric surgery) study

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Complete List of Authors:	Wu, Robert; The Ottawa Hospital, Haggar, Fatima; The Ottawa Health Research Institute, Porte, N'Gai; Pembroke Hospital Civic Campus, Eipe, Naveen; The Ottawa Hospital, Anesthesia Raiche, Isabelle; The Ottawa Hospital Civic Campus, Surgery Neville, Amy; The Ottawa Hospital Civic Campus, Surgery Yelle, Jean Dennis; The Ottawa Hospital Civic Campus, Surgery Ramsay, Tim; The Ottawa Health Research Institute, Mamazza, Joseph; The Ottawa Hospital Civic Campus, Surgery
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Title Page

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Robert Wu, The Ottawa Hospital General Campus, 501 Smyth Rd., Ottawa, Ontario, rowu@toh.on.ca

Fatima Haggar, The Ottawa Health Research Institute, 1053 Carling Ave. Ottawa, Ontario, fhaggar@toh.on.ca

N'Gai Porte, Pembroke Hospital Civic Campus, 201 Deacon Street, Pembrooke, Ontario, ngai.porte@gmail.com

Naveen Eipe, The Ottawa Hospital Civic Campus, 1503 Carling Rd. Ottawa, Ontario, neipe@toh.on.ca

Isabelle Raiche, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, iraiche@toh.on.ca

Amy Neville, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, aneville@toh.on.ca

Jean Denis Yelle, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, jdyelle@toh.on.ca

Tim Ramsay, The Ottawa Health Research Institute, 501 Smyth Rd. Ottawa, Ontario, tramsay@ohri.ca

Joseph Mamazza, The Ottawa Hospital, 1503 Carling Rd. Ottawa, Ontario, jmamazza@toh.on.ca

Corresponding author

Dr. Joseph Mamazza

The Ottawa Hospital-Civic Campus CPC, Suite 328

1503 Carling Rd. Ottawa, Ontario,

K1Y 4E9

Phone: 613-798-5555 ext. 13151

Email: jmamazza@toh.on.ca

ABSTRACT

Introduction

Postoperative pain control remains a major challenge for many surgical procedures, including laparoscopic gastric bypass. Pain management is particularly relevant in obese patients who typically experience a higher number of cardiovascular and pulmonary events. Effective pain management may reduce their risk of serious postoperative complication, such as deep vein thrombosis and pulmonary emboli. The objective of this study is to evaluate the efficacy of intraperitoneal local anesthetic, Ropivicaine, to reduce post-operative pain in patients undergoing laparoscopic Roux-en-Y gastric bypass surgery.

Methods and Analysis

A randomised controlled trial will be conducted to compare intraperitoneal ropivacaine (intervention) versus normal saline (placebo) in 120 adult patients undergoing bariatric bypass surgery. Ropivacaine will be infused over the esophageal hiatus and throughout the abdomen. Patients in the control arm will undergo the same treatment with normal saline. The primary endpoint will be post-operative pain at 1, 2, and 4 hours post-operatively. Pain measurements will then occur every 4 hours for 24 hours and every 8 hours until discharge. Secondary endpoints will include opioid use, peak expiratory flow, 6-minute walk distance, and quality of life assessed in the immediate post-operative period. Intention to treat analysis will be used and repeated measures will be analysed using mixed modelling approach. Post-hoc pairwise comparison of the treatment groups at different time points will be done using multiple comparisons with adjustment to the type1 error rate. Results of the study will inform the feasibility of recruitment and inform sample size of a larger definitive randomized trial to evaluate the effectiveness of intraperitoneal ropivacaine.

Ethics and dissemination

This study has been approved by the Ottawa Health Science Network Research Ethics Board and Health Canada in April 2014. The findings of the study will be disseminated through national and international conferences, as well as peer-reviewed journals.

Trial registration: clinicaltrial.gov 717602410

FOCUS OF STUDY

- We hypothesize the use of intraperitoneal ropivacaine would reduce postoperative pain in the bariatric bypass population and potentially lead to reduced opioid consumption, improved lung function, mobility, and quality of recovery.

STRENGTHS & LIMITATIONS

- The study will have an impact on use of intraperitoneal local anesthetic (IPLA) in laparoscopic gastric bypass surgery. A positive finding would confirm the effectiveness of IPLA in laparoscopic gastric bypass surgery. Negative results may lead to changes to the current postoperative management practices and prompt further research to improve pain management following laparoscopic gastric bypass.

- The study is a single center study. Patients will be subject to standardized intraoperative anesthetic use and postoperative surgical pathway. Generalizability of the study will depend on the practice of individual institution.

INTRODUCTION

Management of post-operative pain remains a major challenge. Effective pain control encourages early ambulation, which significantly reduces the risk of deep vein thrombosis (DVT) and pulmonary emboli (PE); enhances patient's ability to take deep breaths to decrease the risk of pulmonary complications (e.g., atelectasis and pneumonia); and decreases the incidence of tachycardia and unnecessary related investigations.

The obesity epidemic has lead to a significant rise in the need for surgical intervention. This recent phenomenon further highlights the importance of understanding the analgesic requirements of the bariatric patient. Pain management is particularly relevant in the obese population given their higher susceptibility for serious perioperative complications from cardiovascular, thromboembolic, pulmonary events. These include a high prevalence of obstructive sleep apnea, hypoxia, respiratory depression and PE, which is the second leading cause of death among bariatric surgery patients [1].

A number of strategies exist for controlling post-operative pain. One such method, intraperitoneal local anesthetic (IPLA), involves the infusion of local anesthetic into the abdomen during surgery. This procedure has been extensively studied in general surgery and gynecology [2–6]. Two systematic reviews have investigated the effectiveness of IPLA as a method of reducing postoperative pain and opioid consumption [7,8]. Although the timing of IPLA administration varied between included studies (i.e. at pre-dissection or at post-dissection), evidence overwhelmingly supports preemptive IPLA [9–11] as it blocks the afferent nerves in the peritoneum before surgical trauma.

Ropivacaine, a newer analgesic, with a better toxicity profile compared with alternatives such as bupivacaine, is currently considered the safest long acting local anesthetic in the market [12]. Two trials comparing the plasma concentration after intravenous use of

ropivacaine versus bupivacaine have demonstrated that ropivacaine requires a higher plasma concentration before toxicity develops [8,13]. Importantly as an IPLA, ropivacaine has been shown to be effective at reducing pain without clinical toxicity [14–18]. Despite promising results, there is still a paucity of studies that have specifically focused on the use of IPLA in the bariatric surgery population [19–22]. To our knowledge, this is the first trial examining the use of ropivacaine in the setting of obesity surgery. Our objective is to evaluate the efficacy of ropivacaine as an IPLA to reduce post-operative pain in patients undergoing laparoscopic Roux-en-Y gastric bypass surgery (LRYGB).

METHODS AND ANALYSIS

Design

This pilot trial is a double-blind, randomized, controlled parallel arm study. Participants, the clinical care team (surgeon and nurses), and outcome assessors will all be concealed from allocation and blinded during the trial. The pilot study will assess the feasibility of a larger definitive study.

Setting and Participants

Participants will be recruited from the Ottawa Civic Hospital, an academic centre serving a catchment area of 1.3 million residents in Eastern Ontario (Ottawa and environs), Canada. LRYGB is the standard operation for obesity in Canada. Patients will be treated by one of three participating expert surgeons (JM, JDY, AN) who routinely perform LRYGB.

Eligible subjects will be adults undergoing laparoscopic Roux-en-Y gastric bypass surgery for obesity who are able to tolerate general anesthetic and pneumoperitoneum, and provide informed consent for the surgery. Patients with chronic pain requiring pre-operative opioids will be included. Exclusion criteria are: 1) patients undergoing planned sleeve gastrectomy (intra-operative to sleeve gastrectomy after IPLA delivery will be included and

analysed using intention-to-treat approach); 2) allergy to local anesthetics; 3) severe underlying cardiovascular disease, including congestive heart failure, conduction abnormalities, and ischemic heart disease; 4) chronic renal disease stage 3 or higher (defined as creatinine clearance less than 60 mL/h); 5) hepatic dysfunction Child-Pugh class B or C; 6) previous foregut surgery, including esophageal, gastric, liver, and pancreas resections.

Recruitment

Eligible participants will initially be identified by a participating surgeon or a nurse from the Ottawa hospital bariatric surgery clinics. If the patient agrees to participate, consent will be obtained by a research assistant (RA), who is independent from the clinical care of patients. The study flow will be shown according to the CONSORT flow chart (figure 1). Baseline data will be captured by the surgeon at the time of enrolment into trial.

Randomization

Participants will be randomized using a computerized simple randomization scheme in a 1:1 ratio to intervention and control arms. Randomization will be performed on the day prior to surgery to allow for the preparation of medication by the Department of Pharmacy. Surgeries booked on Monday will be randomized on Friday.

Allocation Concealment

Once randomized, pharmacy will independently prepare the treatment solution (Ropivacaine or Normal Saline) in a standardized 100 mL bag. The treatment solution will be attached a patient's unique identifier and will not indicate which arm the patient is allocated. IV bags will be labelled according to Health Canada regulations and will not disclose content contained in the bag. The treatment medication will be delivered to the operating room on the day of surgery.

Blinding

All parties, including the patients, surgeons, clinic/OR/floor unit nurses will be blinded to treatment arm.

Interventions

Study subjects will be randomized into two parallel arms. The patients assigned to the intervention arm will receive the following treatment:

The abdomen will be entered and trocars placed in the usual manner. All patients will receive a total of 100 mL of 0.2% ropivacaine. Using a standard suction/irrigation device and tubing, 200 mg total of Ropivacaine in 100 mL Normal Saline (NS) will be instilled into the abdomen prior to surgical dissection. Under direct visualization, 50 mL will be delivered over the esophageal hiatus. The remaining 50 mL will be infused throughout the abdomen. The infusion line will then be flushed with 30 mL of NS to ensure any residual ropivacaine is delivered. The remainder of the surgery will proceed as usual.

Patients assigned to the control arm will only receive intraperitoneal NS with the same delivery procedure.

Patients in both arms will receive standardized anaesthetic protocol for induction and maintenance. Postoperatively, patients will receive breakthrough pain medication, as necessary, including morphine, hydromorphone, and acetaminophen. All participants will undergo the bariatric surgery clinical pathway.

Outcome Assessment

Baseline data of patient will include demographics, existing co-morbidities, past medical and surgical history, medications, allergies and social history including smoking, alcohol and drug use. Past pain history of fibromyalgia, back pain, and arthritis will be documented.

The patient will also be asked to complete a quality of recovery questionnaire (QR40) and complete a walk test.

Feasibility measures and the decision to proceed with the definitive trial will be determined by number of eligible patients, rates of recruitment, randomization, data completion and quality, patient retention, and cost-related data collection. The required sample size for a definitive trial will be calculated using the clinical outcome data from the pilot trial. The pilot study will be deemed feasible if the number of eligible, randomized, and retained within the pilot trial generate the require sample size within a 12 month period of recruitment. A more than 60% recruitment of those eligible will be seen as acceptable and 90% as satisfactory.

Efficacy endpoint

The data collection and questionnaires to be administered in the pilot trial are those proposed for the definitive trial. The primary efficacy endpoint is post-operative pain score, as measured by the visual analogue scale (VAS), which has been extensively validated in pain management. Changes between 13-16mm are widely accepted as clinically relevant [23].

The secondary efficacy endpoints include: 1) opioid use, as measured by total opioid consumption. Opioid use has been evaluated in other studies where IPLA was used. Some evidence indicate IPLA may significantly reduce the consumption of opioid[19]. 2) Peak expiratory flow (PEF), as measured by the incentive spirometry. PEF has not been studied in obese patients. There is no recommendation on a clinically significant change. 3) 6-min walk distance (6 MWD), defined as the distance (in meters) 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. Clinically significant differences occur at a minimum of 80m [24].

Pain scores will be measured at baseline, immediately in recovery, at 1, 2 and 4 hours post-operation and then every 4 hours for 24 hours, then every 8 hours up to a maximum of 48 hours post-operation. Opioid consumption will be measured immediately after the surgery, then at 1, 2, 4, 12, 24, and then 48 hours or sooner if patient is discharged earlier. PEF scores will be measured at baseline, immediately in recovery and then every four hours for a period of 24 hours, then every 8 hours up to a maximum of 24 hours post-surgery. 6 MWD will be measured at the baseline, on postoperative days one and two and at follow-up clinic within 10 days of operation.

Explanatory endpoint

Quality of life as measured by the QR-40 will be measured. It is a validated instrument that was developed specifically for post-operative patients [25].

QR-40 scores will be recorded at baseline, prior to discharge and at clinic follow-up within 10 days of discharge.

Sample Size

There is relatively little information on the distribution of pain scores, health-related quality of life scores, or on recruitment and retention rates in the obese patient population. The main purpose of the proposed pilot trial is to define the distribution in outcome measures, as well as the feasibility of recruiting and retaining patients for a more definitive trial.

The sample size for pilot trials is typically determined pragmatically, with recommendations of 30-60 participants per arm. Based on a loss to follow-up of 10% with

95% CI of 12.7%-16.3%, we anticipate a recruitment rate of 33 to 38 patients per month to a total of 120 subjects within a four month recruitment period.

DATA ANALYSIS PLAN

The primary and secondary efficacy analysis will be based on the assigned treatment of patients (intention to treat analysis). Efficacy measures will be analysed using a mixed modelling approach to account for the dependence between measurements taken over time from the same patient. The comparison of the treatment arms for the efficacy endpoints will be conducted at a two-sided significance level of 0.05. Post-hoc pair wise comparison of the treatment arms at different time points will be done using multiple comparisons with adjustment to the type I error rate.

QR-40 will be analysed by various cross-tabulations, confidence intervals and proper graphical displays. Parametric and non-parametric correlation coefficients scatter plots and box-whisker plots will be studied. Measurements over-time will be summarized at each interval. QR-40 over time will be compared between treatment arms.

Outcome assessors involved in the measuring and collecting of study endpoints will be blinded to the intervention.

ETHICS AND DISSEMINATION

The Ottawa Health Science Network Research Ethics Board has approved the study and all participants will be provided informed consent.

The study results will be made publically available through local, national, and international conferences, as well as peer-reviewed journals.

DISCUSSION

Outcomes of this pilot trial will determine the feasibility of a larger randomized controlled trial. Recruitment rates, logistics of randomization, treatment allocation, and data acquisition will all be used to assess the feasibility of the definitive study. Evidence of reduced post-operative pain offer great benefit to patient care and quality of life. It provides surgeons and anaesthesiologists with further opportunity to improve patient comfort and; reduce complications, reduce length of stay and healthcare costs. On the other hand, if our study finds evidence to indicate equivalence between IPLA and control arms in postoperative pain control, the already established use of Ropivicaine by many clinics in North America and Europe, would be challenged.

REFERENCES:

1 Fernandez AZ, Demaria EJ, Tichansky DS, *et al.* Multivariate Analysis of Risk Factors for Death Following Gastric Bypass for Treatment of Morbid Obesity. *Ann Surg* 2004;**239**:698–703. doi:10.1097/01.sla.0000124295.41578.ab

2 Narchi P, Benhamou D, Fernandez H. Intraperitoneal local anaesthetic for shoulder pain after day-case laparoscopy. *Lancet* 1991;**338**:1569–70. doi:10.1016/0140-6736(91)92384-E

3 Bisgaard T, Klarskov B, Kristiansen VB, *et al.* Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 1999;**89**:1017–24.http://www.ncbi.nlm.nih.gov/pubmed/10512282 (accessed 4 Oct2013).

4 El-Sherbiny W, Saber W, Askalany AN, *et al.* Effect of intra-abdominal instillation of lidocaine during minor laparoscopic procedures. *Int J Gynaecol Obstet* 2009;**106**:213–5. doi:10.1016/j.ijgo.2009.04.016

5 Kang H, Kim B-G. Intraperitoneal ropivacaine for effective pain relief after laparoscopic appendectomy: a prospective, randomized, double-blind, placebo-controlled study. *J Int Med Res*;**38**:821–32.http://www.ncbi.nlm.nih.gov/pubmed/20819419 (accessed 11 Oct2013).

6 Kahokehr A, Sammour T, Shoshtari KZ, *et al.* Intraperitoneal local anesthetic improves recovery after colon resection: a double-blinded randomized controlled trial. *Ann Surg* 2011;**254**:28–38. doi:10.1097/SLA.0b013e318221f0cf

7 Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. *Anesth Analg* 2006;**103**:682–8. doi:10.1213/01.ane.0000226268.06279.5a

8 Marks JL, Ata B, Tulandi T. Systematic review and metaanalysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. *J Minim Invasive Gynecol*;**19**:545–53. doi:10.1016/j.jmig.2012.04.002

9 Pappas-Gogos G, Tsimogiannis KE, Zikos N, *et al.* Preincisional and intraperitoneal ropivacaine plus normal saline infusion for postoperative pain relief after laparoscopic cholecystectomy: a randomized double-blind controlled trial. *Surg Endosc* 2008;**22**:2036–45. doi:10.1007/s00464-008-9762-x

10 Gupta A. Local anaesthesia for pain relief after laparoscopic cholecystectomy--a systematic review. *Best Pract Res Clin Anaesthesiol* 2005;**19**:275–92.http://www.ncbi.nlm.nih.gov/pubmed/15966498 (accessed 1 Oct2013).

11 Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. *Anesthesiology* 2006;**104**:835–46.http://www.ncbi.nlm.nih.gov/pubmed/16571981 (accessed 11 Oct2013).

12 Graf BM. The cardiotoxicity of local anesthetics: the place of ropivacaine. *Curr Top Med Chem* 2001;**1**:207–14.http://www.ncbi.nlm.nih.gov/pubmed/11895138 (accessed 11 Oct2013).

13 Knudsen K, Beckman Suurküla M, Blomberg S, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997;**78**:507–14.http://www.ncbi.nlm.nih.gov/pubmed/9175963 (accessed 11 Oct2013).

14 Callesen T, Hjort D, Mogensen T, *et al.* Combined field block and i.p. instillation of ropivacaine for pain management after laparoscopic sterilization. *Br J Anaesth* 1999;**82**:586–90.http://www.ncbi.nlm.nih.gov/pubmed/10472228 (accessed 11 Oct2013).

15 Labaille T, Mazoit JX, Paqueron X, *et al.* The clinical efficacy and pharmacokinetics of intraperitoneal ropivacaine for laparoscopic cholecystectomy. *Anesth Analg* 2002;**94**:100–5, table of contents.http://www.ncbi.nlm.nih.gov/pubmed/11772809 (accessed 4 Oct2013).

16 Kucuk C, Kadiogullari N, Canoler O, *et al.* A placebo-controlled comparison of bupivacaine and ropivacaine instillation for preventing postoperative pain after laparoscopic cholecystectomy. *Surg Today* 2007;**37**:396–400. doi:10.1007/s00595-006-3408-1

17 Park YH, Kang H, Woo YC, *et al.* The effect of intraperitoneal ropivacaine on pain after laparoscopic colectomy: a prospective randomized controlled trial. *J Surg Res* 2011;**171**:94–100. doi:10.1016/j.jss.2010.03.024

18 Cha SM, Kang H, Baek CW, *et al.* Peritrocal and intraperitoneal ropivacaine for laparoscopic cholecystectomy: a prospective, randomized, double-blind controlled trial. *J Surg Res* 2012;**175**:251–8. doi:10.1016/j.jss.2011.04.033

19 Symons JL, Kemmeter PR, Davis AT, *et al.* A double-blinded, prospective randomized controlled trial of intraperitoneal bupivacaine in laparoscopic Roux-en-Y gastric bypass. *J Am Coll Surg* 2007;**204**:392–8. doi:10.1016/j.jamcollsurg.2006.12.013

20 Alkhamesi NA, Kane JM, Guske PJ, *et al.* Intraperitoneal aerosolization of bupivacaine is a safe and effective method in controlling postoperative pain in laparoscopic Roux-en-Y gastric bypass. *J Pain Res* 2008;**1**:9–13.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3004614&tool=pmcentrez&rendertype=abstract (accessed 11 Oct2013).

21 Sherwinter DA, Ghaznavi AM, Spinner D, *et al.* Continuous infusion of intraperitoneal bupivacaine after laparoscopic surgery: a randomized controlled trial. *Obes Surg* 2008;**18**:1581–6. doi:10.1007/s11695-008-9628-2

22 Rodriguez L. Intraperitoneal analgesia compared with levobupivacaine 0.25% versus saline in laparoscopic bariatric surgery: 14AP5-11. *Eur J Anaesthesiol* 2011;**28**.

23 Gallagher EJ, Bijur PE, Latimer C, *et al.* Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *Am J Emerg Med* 2002;**20**:287–90.http://www.ncbi.nlm.nih.gov/pubmed/12098173 (accessed 11 Oct2013).

24 Larsson UE, Reynisdottir S. The six-minute walk test in outpatients with obesity: reproducibility and known group validity. *Physiother Res Int* 2008;**13**:84–93. doi:10.1002/pri.398

25 Myles PS, Weitkamp B, Jones K, *et al.* Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth* 2000;**84**:11–5.http://www.ncbi.nlm.nih.gov/pubmed/10740540 (accessed 14 Oct2013).

AUTHORS CONTRIBUTIONS

RW made contributions to study design, was involved in coordinating and overseeing the trial, and drafted the manuscript.

FH made substantial contributions to conception and design, was involved in coordinating the trial and writing and revising the manuscript.

NP and NE made substantial contributions to conception and design. They were involved in organizing the trial.

IR, JDY, AN were involved in organizing the trial. They were also involved in revising the manuscript.

TR made significant contributions to study design and statistical analysis.

JM made contributions to study design, was involved in overseeing the trial, revising the manuscript, and has given the final approval of the version to be published

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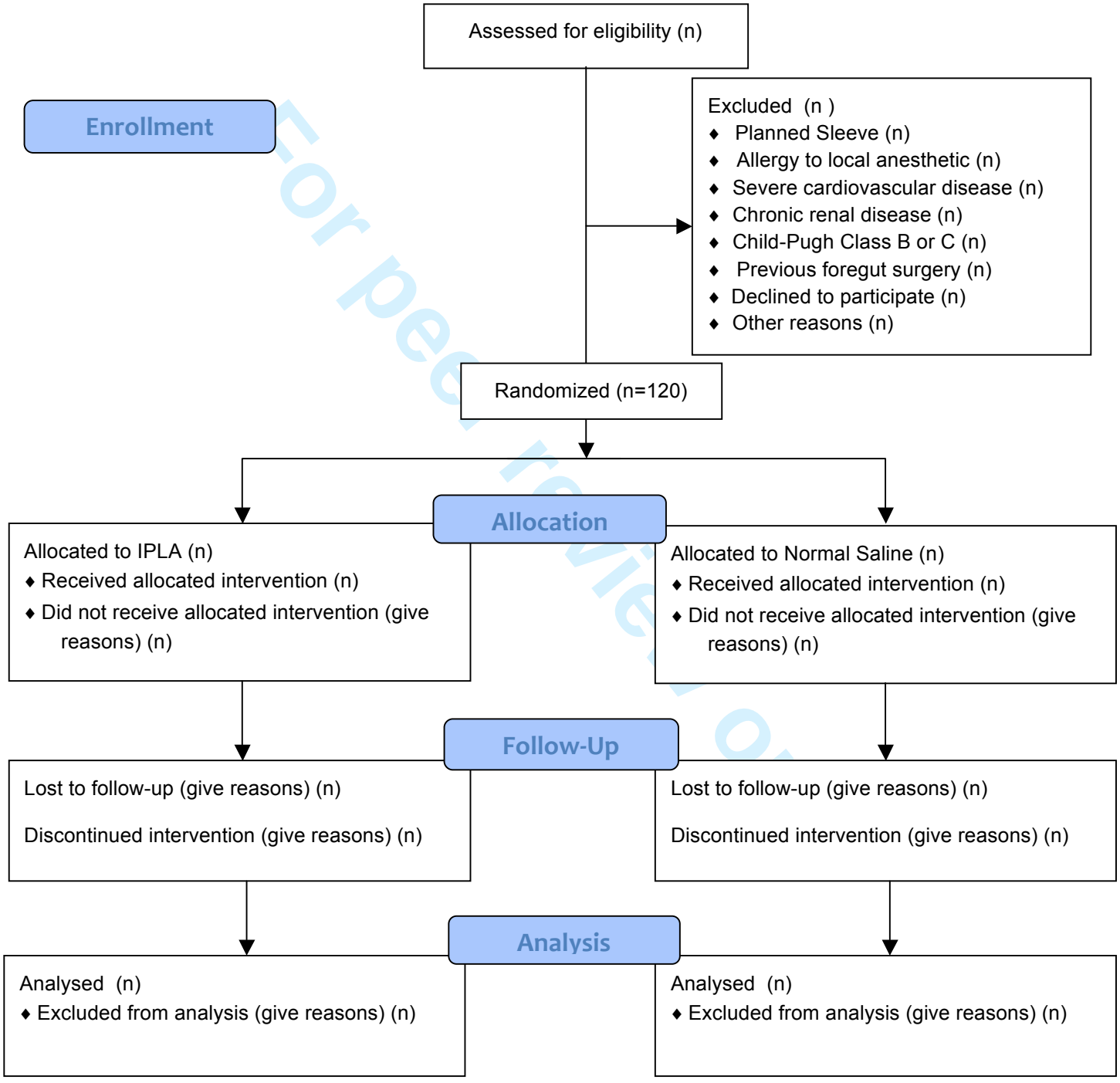
COMPETING INTEREST

The authors declare that they have no competing interests.

Acknowledgement

We thank Hadi Mehrzad Namazi for helping with the database creation of the study. We thank Dong Vo of the Ottawa Health Research Institute for creating the randomization scheme and database for the trial.

Figure 1. CONSORT Flow Diagram of the INOPAIN Study



Source: Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-91.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	_____
	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	15
	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)	N/A

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	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
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, noninferiority, 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	5
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)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	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	7-9
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)	_____

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	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	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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	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	N/A
	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	N/A

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	10
Statistical methods	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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	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)	_____
Methods: Monitoring			
Data monitoring	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	_____
	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	N/A
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	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
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	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
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	_____
Dissemination policy	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	_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Assessing the Feasibility of a Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Intra-Peritoneal Ropivacaine in Gastric Bypass Surgery: a protocol

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Title Page

Assessing the Feasibility of a Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Intra-Peritoneal Ropivacaine in Gastric Bypass Surgery: a protocol

Robert Wu, The Ottawa Hospital General Campus, 501 Smyth Rd., Ottawa, Ontario, rowu@toh.on.ca

Fatima Haggar, The Ottawa Health Research Institute, 1053 Carling Ave. Ottawa, Ontario, fhaggar@toh.on.ca

N'Gai Porte, Pembroke Hospital Civic Campus, 201 Deacon Street, Pembrooke, Ontario, ngai.porte@gmail.com

Naveen Eipe, The Ottawa Hospital Civic Campus, 1503 Carling Rd. Ottawa, Ontario, neipe@toh.on.ca

Isabelle Raiche, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, iraiche@toh.on.ca

Amy Neville, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, aneville@toh.on.ca

Jean Denis Yelle, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, jdyelle@toh.on.ca

Tim Ramsay, The Ottawa Health Research Institute, 501 Smyth Rd. Ottawa, Ontario, tramsay@ohri.ca

Joseph Mamazza, The Ottawa Hospital, 1503 Carling Rd. Ottawa, Ontario, jmamazza@toh.on.ca

Corresponding author

Dr. Joseph Mamazza

The Ottawa Hospital-Civic Campus CPC, Suite 328

1503 Carling Rd. Ottawa, Ontario,

K1Y 4E9

Phone: 613-798-5555 ext. 13151

Email: jmamazza@toh.on.ca

ABSTRACT

Introduction

Postoperative pain control remains a major challenge for surgical procedures, including laparoscopic gastric bypass. Pain management is particularly relevant in obese patients who experience a higher number of cardiovascular and pulmonary events. Effective pain management may reduce their risk of serious postoperative complication, such as deep vein thrombosis and pulmonary emboli. The objective of this study is to evaluate the efficacy of intraperitoneal local anesthetic, Ropivicaine, to reduce post-operative pain in patients undergoing laparoscopic Roux-en-Y gastric bypass.

Methods and Analysis

A randomised controlled trial will be conducted to compare intraperitoneal ropivacaine (intervention) versus normal saline (placebo) in 120 adult patients undergoing bariatric bypass surgery. Ropivacaine will be infused over the esophageal hiatus and throughout the abdomen. Patients in the control arm will undergo the same treatment with normal saline. The primary endpoint will be post-operative pain at 1, 2, and 4 hours post-operatively. Pain measurements will then occur every 4 hours for 24 hours and every 8 hours until discharge. Secondary endpoints will include opioid use, peak expiratory flow, 6-minute walk distance, and quality of life assessed in the immediate post-operative period. Intention to treat analysis will be used and repeated measures will be analysed using mixed modelling approach. Post-hoc pairwise comparison of the treatment groups at different time points will be done using multiple comparisons with adjustment to the type1 error. Results of the study will inform the feasibility of recruitment and inform sample size of a larger definitive randomized trial to evaluate the effectiveness of intraperitoneal ropivacaine.

Ethics and dissemination

This study has been approved by the Ottawa Health Science Network Research Ethics Board and Health Canada in April 2014. The findings of the study will be disseminated through national and international conferences and peer-reviewed journals.

Trial registration: clinicaltrial.gov NCT02154763

Trial sponsor: The Ottawa Health Research Institute

FOCUS OF STUDY

- We hypothesize the use of intraperitoneal ropivacaine would reduce postoperative pain in the bariatric bypass population and potentially lead to reduced opioid consumption, improved lung function, mobility, and quality of recovery.

STRENGTHS & LIMITATIONS

- The study will have an impact on the use of intraperitoneal local anesthetic (IPLA) in laparoscopic gastric bypass surgery. A positive finding would confirm the effectiveness of IPLA in laparoscopic gastric bypass surgery. Negative results may lead to changes to the current postoperative management practices and prompt further research to improve pain management following laparoscopic gastric bypass.

- The study is a single center study. Patients will be subject to standardized intraoperative anesthetic use and postoperative surgical pathway. Generalizability of the study will depend on the practice of individual institution.

INTRODUCTION

Management of post-operative pain remains a major challenge. Effective pain control encourages early ambulation, which significantly reduces the risk of deep vein thrombosis (DVT) and pulmonary emboli (PE); enhances patient's ability to take deep breaths to decrease the risk of pulmonary complications (e.g., atelectasis and pneumonia); and decreases the incidence of tachycardia and unnecessary related investigations.

The obesity epidemic has led to a significant rise in the need for surgical intervention. This recent phenomenon further highlights the importance of understanding the analgesic requirements of the bariatric patient. Pain management is particularly relevant in the obese population given their higher susceptibility for serious perioperative complications from cardiovascular, thromboembolic, pulmonary events. These include a high prevalence of obstructive sleep apnea, hypoxia, respiratory depression and PE, which is the second leading cause of death among bariatric surgery patients [1].

A number of strategies exist for controlling post-operative pain. One such method, intraperitoneal local anesthetic (IPLA), involves the infusion of local anesthetic into the abdomen during surgery. This procedure has been extensively studied in general surgery and gynecology [2–6]. Two systematic reviews have investigated the effectiveness of IPLA as a method of reducing postoperative pain and opioid consumption [7,8]. Although the timing of IPLA administration varied between included studies (i.e. at pre-dissection or at post-dissection), evidence overwhelmingly supports preemptive IPLA [9–11] as it blocks the afferent nerves in the peritoneum before surgical trauma.

Ropivacaine, a newer analgesic, with a better toxicity profile compared with alternatives such as bupivacaine, is currently considered the safest long acting local anesthetic in the market [12]. Two trials comparing the plasma concentration after intravenous use of

ropivacaine versus bupivacaine have demonstrated that ropivacaine requires a higher plasma concentration before toxicity develops [8,13]. Importantly as an IPLA, ropivacaine has been shown to be effective at reducing pain without clinical toxicity [14–18]. Despite promising results, there is still a paucity of studies that have specifically focused on the use of IPLA in the bariatric surgery population [19–22]. To our knowledge, this is the first trial examining the use of ropivacaine in the setting of obesity surgery. Our objective is to evaluate the efficacy of ropivacaine as an IPLA to reduce post-operative pain in patients undergoing laparoscopic Roux-en-Y gastric bypass surgery (LRYGB).

METHODS AND ANALYSIS

Design

The study recruitment began on July 3rd and is expected to last 6 months to Dec 31 2014. This pilot trial is a double-blind, randomized, controlled parallel arm study. Participants, the clinical care team (surgeon and nurses), and outcome assessors will all be concealed from allocation and blinded during the trial. The pilot study will assess the feasibility of a larger definitive study.

Setting and Participants

Participants will be recruited from the Ottawa Civic Hospital, an academic centre serving a catchment area of 1.3 million residents in Eastern Ontario (Ottawa and environs), Canada. LRYGB is the standard operation for obesity in Canada. Patients will be treated by one of three participating expert surgeons (JM, JDY, AN) who routinely perform LRYGB.

Eligible subjects will be adults undergoing laparoscopic Roux-en-Y gastric bypass surgery for obesity who are able to tolerate general anesthetic and pneumoperitoneum, and provide informed consent for the surgery. Patients with chronic pain requiring pre-operative opioids will be included. Exclusion criteria are: 1) patients undergoing planned sleeve

gastrectomy (intra-operative conversion to sleeve gastrectomy after IPLA delivery will be included and analysed using intention-to-treat approach); 2) allergy to local anesthetics; 3) severe underlying cardiovascular disease, including congestive heart failure, conduction abnormalities, and ischemic heart disease; 4) chronic renal disease stage 3 or higher (defined as creatinine clearance less than 60 mL/h); 5) hepatic dysfunction Child-Pugh class B or C; 6) previous foregut surgery, including esophageal, gastric, liver, and pancreas resections.

Recruitment

Eligible participants will initially be identified by a participating surgeon or a nurse from the Ottawa hospital bariatric surgery clinic. If the patient agrees to participate, consent will be obtained by a research assistant (RA), who is independent from the clinical care of patients. The study flow will be shown according to the CONSORT flow chart (figure 1). Baseline data will be captured by the surgeon at the time of enrolment into trial.

Randomization

Participants will be randomized using a computerized simple randomization scheme in a 1:1 ratio to intervention and control arms. Randomization will be performed on the day prior to surgery to allow for the preparation of medication by the Department of Pharmacy. Surgeries booked on Monday will be randomized on Friday.

Allocation Concealment

Once randomized, pharmacy will independently prepare the treatment solution (Ropivacaine or Normal Saline) in a standardized 100 mL bag. The treatment solution will be attached a patient's unique identifier and will not indicate which arm the patient is allocated. IV bags will be labelled according to Health Canada regulations and will not

disclose content contained in the bag. The treatment medication will be delivered to the operating room on the day of surgery.

Blinding

All parties, including the patients, surgeons, clinic/OR/floor unit nurses will be blinded to treatment arm. 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, the event will be recorded in the patient's chart and study file with the corresponding reason for un-blinding .

Interventions

Study subjects will be randomized into two parallel arms. The patients assigned to the intervention arm will receive the following treatment:

The abdomen will be entered and trocars placed in the usual manner. All patients will receive a total of 100 mL of 0.2% ropivacaine. Using a standard suction/irrigation device and tubing, 200 mg total of Ropivacaine in 100 mL Normal Saline (NS) will be instilled into the abdomen prior to surgical dissection. Under direct visualization, 50 mL will be delivered over the esophageal hiatus. The remaining 50 mL will be infused throughout the abdomen. The infusion line will then be flushed with 30 mL of NS to ensure any residual ropivacaine is delivered. The remainder of the surgery will proceed as usual. Patients assigned to the control arm will only receive intraperitoneal NS with the same delivery procedure.

The effect of irrigation and suction is unlikely to impact the absorption of Ropivacaine unless the infused fluid is suctioned immediately. It has a high absorption constant and is rapidly taken up systemically [23]. There is ample research support for the pre-emptive delivery of anesthetic prior to dissection [9–11]. The intraperitoneal absorption of

Ropivacaine and plasma concentration has been studied and shown to have low toxicity potential where the peak concentration was much less (1.14 ug/ml) than the maximum tolerable level of 2.2 mg/L [24]. To ensure operator compliance, each delivered package to the operating theatre will be checked to ensure all assigned medication was delivered.

Patients in both arms will receive standardized anaesthetic protocol for induction and maintenance. Induction anaesthetic would only include fentanyl boluses for pain, ketamine or propofol for sedation, and rocuronium or succinylcholine for neuromuscular blockade. For general anesthesia maintenance, dexmedetomidine and fentanyl boluses are to be used. Dexamethasone and ondansetron will be used as intraoperative antiemetics. No long acting opioids will be used pre- or intra-operatively. Postoperatively, patients will receive breakthrough pain medication, as necessary, including morphine, hydromorphone, and acetaminophen. All participants will undergo the bariatric surgery clinical pathway.

Outcome Assessment

Baseline data will include patient demographics and their existing co-morbidities, past medical and surgical history, medications, allergies and social history including smoking, alcohol and drug use. Past pain history of fibromyalgia, back pain, and arthritis will be documented. The patient will also be asked to complete a quality of recovery questionnaire (QR40) and a 6-minute walk test.

Feasibility measures and the decision to proceed with the definitive trial will be determined by number of eligible patients, rates of recruitment, randomization, data completion and quality, patient retention, and cost-related data collection. The required sample size for a definitive trial will be calculated using the clinical outcome data from the pilot trial. The pilot study will be deemed feasible if the number of eligible, randomized, and retained within the pilot trial generate the require sample size within a 12 month period of

recruitment. A more than 60% recruitment of those eligible will be seen as acceptable and 90% as satisfactory.

Efficacy endpoint

The data collection and questionnaires to be administered in the pilot trial are those proposed for the definitive trial. The primary efficacy endpoint is post-operative pain score, as measured by the visual analogue scale (VAS), which has been extensively validated in pain management. Changes between 13-16mm are widely accepted as clinically relevant [25].

The secondary efficacy endpoints include: 1) opioid use, as measured by total opioid consumption. The quantity and route of opioid medication delivery will be captured and converted to morphine equivalent for comparison. Opioid use has been evaluated in other studies where IPLA was used. Some evidence indicate IPLA may significantly reduce the consumption of opioid[19]. Acetaminophen will be administered orally and overall consumption will be captured. 2) Peak expiratory flow (PEF), as measured by the incentive spirometry. PEF has not been studied in obese patients. There is no recommendation on a clinically significant change. 3) 6-min walk distance (6 MWD), defined as the distance (in meters) 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. Clinically significant differences occur at a minimum of 80m [26].

Pain scores will be measured at baseline, immediately in recovery, at 1, 2 and 4 hours post-operation and then every 4 hours for 24 hours, then every 8 hours up to a maximum of 48 hours post-operation. Opioid consumption will be measured immediately after the surgery, then at 1, 2, 4, 12, 24, and then 48 hours or sooner if patient is discharged earlier. PEF scores will be measured at baseline, immediately in recovery and then every four hours for

a period of 24 hours, then every 8 hours up to a maximum of 24 hours post-surgery. 6 MWD will be measured at the baseline, on postoperative days one and two and at follow-up clinic within 10 days of operation.

Explanatory endpoint

Quality of life as measured by the QR-40 will be measured. It is a validated instrument that was developed specifically for post-operative patients [27].

QR-40 scores will be recorded at baseline, prior to discharge and at clinic follow-up within 10 days of discharge.

Study Flow

An overview of planned data collection is demonstrated in table 1.

Sample Size

There is relatively little information on the distribution of pain scores, health-related quality of life scores, or on recruitment and retention rates in the obese patient population. The main purpose of the proposed pilot trial is to define the distribution in outcome measures, as well as the feasibility of recruiting and retaining patients for a more definitive trial.

The sample size for pilot trials is typically determined pragmatically, with recommendations of 30-60 participants per arm. Based on a loss to follow-up of 10% with 95% CI of 12.7%-16.3%, we anticipate a recruitment rate of 33 to 38 patients per month to a total of 120 subjects within a four month recruitment period.

RESCUE MEDICATION AND RISK MANAGEMENT

The organization, monitoring, quality assurance will be under the responsibility of the principal investigator.

Peak serum concentration of the Ropivacaine occurs 30 minutes after instillation [15] and decreases thereafter. Patients will receive standard cardiorespiratory monitoring, 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 to 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. 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.

DISCONTINUATION CRITERIA

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.

DATA SAFETY MONITORING

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 DSMD will perform ongoing review of safety and efficacy data to minimize exposure of patients to unsafe therapy or dose, make recommendations for changes in the study processes where appropriate, advise on the need for dose adjustment for safety issues, and endorse study continuation.

The sponsoring organization, the Ottawa Health Research Institute (OHRI) will also internally audit the trial conduct at the beginning and every 3 months during the trial.

DATA COLLECTION AND ANALYSIS PLAN

Research assistants will collect majority of the data and nurses on the bariatric floor will also help collect pain score and peak expiratory flow while patients are recovering in the bariatric unit. Nurse educator, nursing unit coordinator in the relevant hospital units have been informed and trained for the study. Research assistants have been trained by the sponsoring OHRI on accuracy and consistency of data collection.

The primary and secondary efficacy analysis will be based on the assigned treatment of patients (intention to treat analysis). Efficacy measures will be analysed using a mixed modelling approach to account for the dependence between measurements taken over time from the same patient. The comparison of the treatment arms for the efficacy endpoints will be conducted at a two-sided significance level of 0.05. Post-hoc pair wise comparison of the treatment arms at different time points will be done using multiple comparisons with adjustment to the type I error rate. No interim analysis is planned for this study.

QR-40 will be analysed by various cross-tabulations, confidence intervals and proper graphical displays. Parametric and non-parametric correlation coefficients scatter plots and box-whisker plots will be studied. Measurements over-time will be summarized at each interval. QR-40 over time will be compared between treatment arms.

Outcome assessors involved in the measuring and collecting of study endpoints will be blinded to the intervention.

The trial data will be housed on the OHRI network and will only be accessible to study investigators and research assistants upon request.

SAFETY

Safety endpoints are:

- Serious adverse event rates– defined as the fraction of subjects with an SAE.
- Surgical complications rates – defined as the fraction of subjects with a surgical complication

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. Serious adverse events are not anticipated in this study.

Safety analysis

The safety efficacy analysis will be based on the treated population. Subjects will be included in the analysis according to the treatment received.

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 preferred term and system organ class. Information regarding the occurrence of surgical complications events will be recorded on 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.

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).

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 for Ropivicaine. An unexpected event for a Ropivicaine 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 Ropivicaine, Health Canada will be notified within 7 calendar days.

Ethics And Dissemination

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has approved the study and all participants will be provided informed consent. All changes to the trial protocol are required to be approved by the OHSN-REB.

Only the study research assistants and individuals in the patient's circle of care will have access to patient information.

The study results will be made publically available through local, national, and international conferences, as well as peer-reviewed journals.

Discussion

Outcomes of this pilot trial will determine the feasibility of a larger randomized controlled trial. Recruitment rates, logistics of randomization, treatment allocation, and data acquisition will all be used to assess the feasibility of the definitive study. Improvement of post-operative pain management offers great benefit to patient care and quality of life. It provides surgeons and anaesthesiologists with further opportunity to improve patient comfort and; reduce complications, reduce length of stay and healthcare costs. On the other hand, if our study finds evidence to indicate equivalence between IPLA and control arms in postoperative pain control, the already established use of Ropivicaine by many clinics in North America and Europe, would be challenged.

Table 1. INOPAIN study flow

	Preop Education Class	Clinic visit with Surgeon	Preop Admit Unit	Operating Room	Postop Anaesthetic Unit	Bariatric floor	Follow-up clinic
Informed consent	X						
Study eligibility confirmation		X					
Demographic data		X					
Medical & surgical history		X					
Height, weight, & BMI		X					
6 Minute Walk Distance		X				X	X
Quality of recovery 40		X				X	X
Pain			X		X	X	
Peak expiratory flow			X		X	X	
Intraoperative anaesthetic use				X			
Intraoperative adverse events and procedures				X			
Postop pain medication use					X	X	
Postoperative events							X

REFERENCES:

1 Fernandez AZ, Demaria EJ, Tichansky DS, *et al.* Multivariate Analysis of Risk Factors for Death Following Gastric Bypass for Treatment of Morbid Obesity. *Ann Surg* 2004;**239**:698–703. doi:10.1097/01.sla.0000124295.41578.ab

2 Narchi P, Benhamou D, Fernandez H. Intraperitoneal local anaesthetic for shoulder pain after day-case laparoscopy. *Lancet* 1991;**338**:1569–70. doi:10.1016/0140-6736(91)92384-E

3 Bisgaard T, Klarskov B, Kristiansen VB, *et al.* Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 1999;**89**:1017–24.http://www.ncbi.nlm.nih.gov/pubmed/10512282 (accessed 4 Oct2013).

4 El-Sherbiny W, Saber W, Askalany AN, *et al.* Effect of intra-abdominal instillation of lidocaine during minor laparoscopic procedures. *Int J Gynaecol Obstet* 2009;**106**:213–5. doi:10.1016/j.ijgo.2009.04.016

5 Kang H, Kim B-G. Intraperitoneal ropivacaine for effective pain relief after laparoscopic appendectomy: a prospective, randomized, double-blind, placebo-controlled study. *J Int Med Res*;**38**:821–32.http://www.ncbi.nlm.nih.gov/pubmed/20819419 (accessed 11 Oct2013).

6 Kahokehr A, Sammour T, Shoshtari KZ, *et al.* Intraperitoneal local anesthetic improves recovery after colon resection: a double-blinded randomized controlled trial. *Ann Surg* 2011;**254**:28–38. doi:10.1097/SLA.0b013e318221f0cf

7 Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. *Anesth Analg* 2006;**103**:682–8. doi:10.1213/01.ane.0000226268.06279.5a

8 Marks JL, Ata B, Tulandi T. Systematic review and metaanalysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. *J Minim Invasive Gynecol*;**19**:545–53. doi:10.1016/j.jmig.2012.04.002

9 Pappas-Gogos G, Tsimogiannis KE, Zikos N, *et al.* Preincisional and intraperitoneal ropivacaine plus normal saline infusion for postoperative pain relief after laparoscopic cholecystectomy: a randomized double-blind controlled trial. *Surg Endosc* 2008;**22**:2036–45. doi:10.1007/s00464-008-9762-x

10 Gupta A. Local anaesthesia for pain relief after laparoscopic cholecystectomy--a systematic review. *Best Pract Res Clin Anaesthesiol* 2005;**19**:275–92.http://www.ncbi.nlm.nih.gov/pubmed/15966498 (accessed 1 Oct2013).

11 Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. *Anesthesiology* 2006;**104**:835–46.http://www.ncbi.nlm.nih.gov/pubmed/16571981 (accessed 11 Oct2013).

12 Graf BM. The cardiotoxicity of local anesthetics: the place of ropivacaine. *Curr Top Med Chem* 2001;**1**:207–14.http://www.ncbi.nlm.nih.gov/pubmed/11895138 (accessed 11 Oct2013).

13 Knudsen K, Beckman Suurküla M, Blomberg S, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997;**78**:507–14.http://www.ncbi.nlm.nih.gov/pubmed/9175963 (accessed 11 Oct2013).

14 Callesen T, Hjort D, Mogensen T, *et al.* Combined field block and i.p. instillation of ropivacaine for pain management after laparoscopic sterilization. *Br J Anaesth* 1999;**82**:586–90.http://www.ncbi.nlm.nih.gov/pubmed/10472228 (accessed 11 Oct2013).

15 Labaille T, Mazoit JX, Paqueron X, *et al.* The clinical efficacy and pharmacokinetics of intraperitoneal ropivacaine for laparoscopic cholecystectomy. *Anesth Analg* 2002;**94**:100–5, table of contents.http://www.ncbi.nlm.nih.gov/pubmed/11772809 (accessed 4 Oct2013).

16 Kucuk C, Kadiogullari N, Canoler O, *et al.* A placebo-controlled comparison of bupivacaine and ropivacaine instillation for preventing postoperative pain after laparoscopic cholecystectomy. *Surg Today* 2007;**37**:396–400. doi:10.1007/s00595-006-3408-1

17 Park YH, Kang H, Woo YC, *et al.* The effect of intraperitoneal ropivacaine on pain after laparoscopic colectomy: a prospective randomized controlled trial. *J Surg Res* 2011;**171**:94–100. doi:10.1016/j.jss.2010.03.024

18 Cha SM, Kang H, Baek CW, *et al.* Peritrocal and intraperitoneal ropivacaine for laparoscopic cholecystectomy: a prospective, randomized, double-blind controlled trial. *J Surg Res* 2012;**175**:251–8. doi:10.1016/j.jss.2011.04.033

19 Symons JL, Kemmeter PR, Davis AT, *et al.* A double-blinded, prospective randomized controlled trial of intraperitoneal bupivacaine in laparoscopic Roux-en-Y gastric bypass. *J Am Coll Surg* 2007;**204**:392–8. doi:10.1016/j.jamcollsurg.2006.12.013

20 Alkhamesi NA, Kane JM, Guske PJ, *et al.* Intraperitoneal aerosolization of bupivacaine is a safe and effective method in controlling postoperative pain in laparoscopic Roux-en-Y gastric bypass. *J Pain Res* 2008;**1**:9–13.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3004614&tool=pmcentrez&rendertype=abstract (accessed 11 Oct2013).

21 Sherwinter DA, Ghaznavi AM, Spinner D, *et al.* Continuous infusion of intraperitoneal bupivacaine after laparoscopic surgery: a randomized controlled trial. *Obes Surg* 2008;**18**:1581–6. doi:10.1007/s11695-008-9628-2

22 Rodriguez L. Intraperitoneal analgesia compared with levobupivacaine 0.25% versus saline in laparoscopic bariatric surgery: 14AP5-11. *Eur J Anaesthesiol* 2011;**28**.

23 Betton D, Greib N, Schlotterbeck H, *et al.* The pharmacokinetics of ropivacaine after intraperitoneal administration: instillation versus nebulization. *Anesth Analg* 2010;**111**:1140–5. doi:10.1213/ANE.0b013e3181f3fb19

24 Maestroni U, Sortini D, Devito C, *et al.* A new method of preemptive analgesia in laparoscopic cholecystectomy. *Surg Endosc* 2002;**16**:1336–40. doi:10.1007/s00464-001-9181-8

25 Gallagher EJ, Bijur PE, Latimer C, *et al.* Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *Am J Emerg Med* 2002;**20**:287–90.http://www.ncbi.nlm.nih.gov/pubmed/12098173 (accessed 11 Oct2013).

26 Larsson UE, Reynisdottir S. The six-minute walk test in outpatients with obesity: reproducibility and known group validity. *Physiother Res Int* 2008;**13**:84–93. doi:10.1002/pri.398

27 Myles PS, Weitkamp B, Jones K, *et al.* Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth* 2000;**84**:11–5.http://www.ncbi.nlm.nih.gov/pubmed/10740540 (accessed 14 Oct2013).

28 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111–7. doi:10.1164/ajrccm.166.1.at1102

AUTHORS CONTRIBUTIONS

RW made contributions to study design, was involved in coordinating and overseeing the trial, and drafted the manuscript.

FH made substantial contributions to conception and design, was involved in coordinating the trial and writing and revising the manuscript.

NP and NE made substantial contributions to conception and design. They were involved in organizing the trial.

IR, JDY, AN were involved in organizing the trial. They were also involved in revising the manuscript.

TR made significant contributions to study design and statistical analysis.

JM made contributions to study design, was involved in overseeing the trial, revising the manuscript, and has given the final approval of the version to be published

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COMPETING INTEREST

The authors declare that they have no competing interests.

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Title Page

A Pilot Study to Assess the Feasibility of a Future Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Role of Intra-Peritoneal Ropivacaine in Gastric Bypass Surgery: the INOPAIN (INtrapertoneal rOPivAcaine IN bariatric surgery) study

Robert Wu, The Ottawa Hospital General Campus, 501 Smyth Rd., Ottawa, Ontario, rowu@toh.on.ca

Fatima Haggar, The Ottawa Health Research Institute, 1053 Carling Ave. Ottawa, Ontario, fhaggar@toh.on.ca

N'Gai Porte, Pembroke Hospital Civic Campus, 201 Deacon Street, Pembrooke, Ontario, ngai.porte@gmail.com

Naveen Eipe, The Ottawa Hospital Civic Campus, 1503 Carling Rd. Ottawa, Ontario, neipe@toh.on.ca

Isabelle Raiche, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, iraiche@toh.on.ca

Amy Neville, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, aneville@toh.on.ca

Jean Denis Yelle, The Ottawa Hospital Civic Campus, 1503 Carling Ave. Ottawa, Ontario, jdyelle@toh.on.ca

Tim Ramsay, The Ottawa Health Research Institute, 501 Smyth Rd. Ottawa, Ontario, tramsay@ohri.ca

Joseph Mamazza, The Ottawa Hospital, 1503 Carling Rd. Ottawa, Ontario, jmamazza@toh.on.ca

Corresponding author

Dr. Joseph Mamazza

The Ottawa Hospital-Civic Campus CPC, Suite 328

1503 Carling Rd. Ottawa, Ontario,

K1Y 4E9

Phone: 613-798-5555 ext. 13151

Email: jmamazza@toh.on.ca

ABSTRACT

Introduction

Postoperative pain control remains a major challenge for ~~many~~ surgical procedures, including laparoscopic gastric bypass. Pain management is particularly relevant in obese patients who ~~typically~~ experience a higher number of cardiovascular and pulmonary events. Effective pain management may reduce their risk of serious postoperative complication, such as deep vein thrombosis and pulmonary emboli. The objective of this study is to evaluate the efficacy of intraperitoneal local anesthetic, Ropivicaine, to reduce post-operative pain in patients undergoing laparoscopic Roux-en-Y gastric bypass ~~surgery~~.

Methods and Analysis

A randomised controlled trial will be conducted to compare intraperitoneal ropivacaine (intervention) versus normal saline (placebo) in 120 adult patients undergoing bariatric bypass surgery. Ropivacaine will be infused over the esophageal hiatus and throughout the abdomen. Patients in the control arm will undergo the same treatment with normal saline. The primary endpoint will be post-operative pain at 1, 2, and 4 hours post-operatively. Pain measurements will then occur every 4 hours for 24 hours and every 8 hours until discharge. Secondary endpoints will include opioid use, peak expiratory flow, 6-minute walk distance, and quality of life assessed in the immediate post-operative period. Intention to treat analysis will be used and repeated measures will be analysed using mixed modelling approach. Post-hoc pairwise comparison of the treatment groups at different time points will be done using multiple comparisons with adjustment to the type1 error ~~rate~~. Results of the study will inform the feasibility of recruitment and inform sample size of a larger definitive randomized trial to evaluate the effectiveness of intraperitoneal ropivacaine.

Ethics and dissemination

This study has been approved by the Ottawa Health Science Network Research Ethics Board and Health Canada in April 2014. The findings of the study will be disseminated through national and international conferences and peer-reviewed journals.

Trial registration: clinicaltrial.gov NCT02154763

Trial sponsor: The Ottawa Health Research Institute

FOCUS OF STUDY

- We hypothesize the use of intraperitoneal ropivacaine would reduce postoperative pain in the bariatric bypass population and potentially lead to reduced opioid consumption, improved lung function, mobility, and quality of recovery.

STRENGTHS & LIMITATIONS

- The study will have an impact on the use of intraperitoneal local anesthetic (IPLA) in laparoscopic gastric bypass surgery. A positive finding would confirm the effectiveness of IPLA in laparoscopic gastric bypass surgery. Negative results may lead to changes to the current postoperative management practices and prompt further research to improve pain management following laparoscopic gastric bypass.

- The study is a single center study. Patients will be subject to standardized intraoperative anesthetic use and postoperative surgical pathway. Generalizability of the study will depend on the practice of individual institution.

INTRODUCTION

Management of post-operative pain remains a major challenge. Effective pain control encourages early ambulation, which significantly reduces the risk of deep vein thrombosis (DVT) and pulmonary emboli (PE); enhances patient's ability to take deep breaths to decrease the risk of pulmonary complications (e.g., atelectasis and pneumonia); and decreases the incidence of tachycardia and unnecessary related investigations.

The obesity epidemic has lead to a significant rise in the need for surgical intervention. This recent phenomenon further highlights the importance of understanding the analgesic requirements of the bariatric patient. Pain management is particularly relevant in the obese population given their higher susceptibility for serious perioperative complications from cardiovascular, thromboembolic, pulmonary events. These include a high prevalence of obstructive sleep apnea, hypoxia, respiratory depression and PE, which is the second leading cause of death among bariatric surgery patients [1].

A number of strategies exist for controlling post-operative pain. One such method, intraperitoneal local anesthetic (IPLA), involves the infusion of local anesthetic into the abdomen during surgery. This procedure has been extensively studied in general surgery and gynecology [2–6]. Two systematic reviews have investigated the effectiveness of IPLA as a method of reducing postoperative pain and opioid consumption [7,8]. Although the timing of IPLA administration varied between included studies (i.e. at pre-dissection or at post-dissection), evidence overwhelmingly supports preemptive IPLA [9–11] as it blocks the afferent nerves in the peritoneum before surgical trauma.

Ropivacaine, a newer analgesic, with a better toxicity profile compared with alternatives such as bupivacaine, is currently considered the safest long acting local anesthetic in the market [12]. Two trials comparing the plasma concentration after intravenous use of

ropivacaine versus bupivacaine have demonstrated that ropivacaine requires a higher plasma concentration before toxicity develops [8,13]. Importantly as an IPLA, ropivacaine has been shown to be effective at reducing pain without clinical toxicity [14–18]. Despite promising results, there is still a paucity of studies that have specifically focused on the use of IPLA in the bariatric surgery population [19–22]. To our knowledge, this is the first trial examining the use of ropivacaine in the setting of obesity surgery. Our objective is to evaluate the efficacy of ropivacaine as an IPLA to reduce post-operative pain in patients undergoing laparoscopic Roux-en-Y gastric bypass surgery (LRYGB).

METHODS AND ANALYSIS

Design

This pilot trial is a double-blind, randomized, controlled parallel arm study. Participants, the clinical care team (surgeon and nurses), and outcome assessors will all be concealed from allocation and blinded during the trial. The pilot study will assess the feasibility of a larger definitive study.

Setting and Participants

Participants will be recruited from the Ottawa Civic Hospital, an academic centre serving a catchment area of 1.3 million residents in Eastern Ontario (Ottawa and environs), Canada. LRYGB is the standard operation for obesity in Canada. Patients will be treated by one of three participating expert surgeons (JM, JDY, AN) who routinely perform LRYGB.

Eligible subjects will be adults undergoing laparoscopic Roux-en-Y gastric bypass surgery for obesity who are able to tolerate general anesthetic and pneumoperitoneum, and provide informed consent for the surgery. Patients with chronic pain requiring pre-operative opioids will be included. Exclusion criteria are: 1) patients undergoing planned sleeve gastrectomy (intra-operative conversion to sleeve gastrectomy after IPLA delivery will be

included and analysed using intention-to-treat approach); 2) allergy to local anesthetics; 3) severe underlying cardiovascular disease, including congestive heart failure, conduction abnormalities, and ischemic heart disease; 4) chronic renal disease stage 3 or higher (defined as creatinine clearance less than 60 mL/h); 5) hepatic dysfunction Child-Pugh class B or C; 6) previous foregut surgery, including esophageal, gastric, liver, and pancreas resections.

Recruitment

Eligible participants will initially be identified by a participating surgeon or a nurse from the Ottawa hospital bariatric surgery clinics. If the patient agrees to participate, consent will be obtained by a research assistant (RA), who is independent from the clinical care of patients. The study flow will be shown according to the CONSORT flow chart (figure 1). Baseline data will be captured by the surgeon at the time of enrolment into trial.

Randomization

Participants will be randomized using a computerized simple randomization scheme in a 1:1 ratio to intervention and control arms. Randomization will be performed on the day prior to surgery to allow for the preparation of medication by the Department of Pharmacy. Surgeries booked on Monday will be randomized on Friday.

Allocation Concealment

Once randomized, pharmacy will independently prepare the treatment solution (Ropivacaine or Normal Saline) in a standardized 100 mL bag. The treatment solution will be attached a patient's unique identifier and will not indicate which arm the patient is allocated. IV bags will be labelled according to Health Canada regulations and will not disclose content contained in the bag. The treatment medication will be delivered to the operating room on the day of surgery.

Blinding

All parties, including the patients, surgeons, clinic/OR/floor unit nurses will be blinded to treatment arm. 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, the event will be recorded in the patient's chart and study file with the corresponding reason for un-blinding .

Interventions

Study subjects will be randomized into two parallel arms. The patients assigned to the intervention arm will receive the following treatment:

The abdomen will be entered and trocars placed in the usual manner. All patients will receive a total of 100 mL of 0.2% ropivacaine. Using a standard suction/irrigation device and tubing, 200 mg total of Ropivacaine in 100 mL Normal Saline (NS) will be instilled into the abdomen prior to surgical dissection. Under direct visualization, 50 mL will be delivered over the esophageal hiatus. The remaining 50 mL will be infused throughout the abdomen. The infusion line will then be flushed with 30 mL of NS to ensure any residual ropivacaine is delivered. The remainder of the surgery will proceed as usual. Patients assigned to the control arm will only receive intraperitoneal NS with the same delivery procedure.

The effect of irrigation and suction is unlikely to impact the absorption of Ropivacaine unless the infused fluid is suctioned immediately. It has a high absorption constant and is rapidly taken up systemically [23]. There is ample research support for the pre-emptive delivery of anesthetic prior to dissection [9–11]. The intraperitoneal absorption of Ropivacaine and plasma concentration has been studied and shown to have low toxicity potential where the peak concentration was much less (1.14 ug/ml) than the maximum

tolerable level of 2.2 mg/L [24]. To ensure operator compliance, each delivered package to the operating theatre will be checked to ensure all assigned medication was delivered.

Patients in both arms will receive standardized anaesthetic protocol for induction and maintenance. Induction anaesthetic would only include fentanyl boluses for pain, ketamine or propofol for sedation, and rocuronium or succinylcholine for neuromuscular blockade. For general anesthesia maintenance, dexmedetomidine and fentanyl boluses are to be used. Dexamethasone and ondansetron will be used as intraoperative antiemetics. No long acting opioids will be used pre- or intra-operatively. Postoperatively, patients will receive breakthrough pain medication, as necessary, including morphine, hydromorphone, and acetaminophen. All participants will undergo the bariatric surgery clinical pathway.

Outcome Assessment

Baseline data ~~of patient~~ will include patient demographics and their ~~,~~ existing co-morbidities, past medical and surgical history, medications, allergies and social history including smoking, alcohol and drug use. Past pain history of fibromyalgia, back pain, and arthritis will be documented. The patient will also be asked to complete a quality of recovery questionnaire (QR40) and ~~complete~~ a 6-minute walk test.

Feasibility measures and the decision to proceed with the definitive trial will be determined by number of eligible patients, rates of recruitment, randomization, data completion and quality, patient retention, and cost-related data collection. The required sample size for a definitive trial will be calculated using the clinical outcome data from the pilot trial. The pilot study will be deemed feasible if the number of eligible, randomized, and retained within the pilot trial generate the require sample size within a 12 month period of recruitment. A more than 60% recruitment of those eligible will be seen as acceptable and 90% as satisfactory.

Efficacy endpoint

The data collection and questionnaires to be administered in the pilot trial are those proposed for the definitive trial. The primary efficacy endpoint is post-operative pain score, as measured by the visual analogue scale (VAS), which has been extensively validated in pain management. Changes between 13-16mm are widely accepted as clinically relevant [25].

The secondary efficacy endpoints include: 1) opioid use, as measured by total opioid consumption. The quantity and route of opioid medication delivery will be captured and converted to morphine equivalent for comparison. Opioid use has been evaluated in other studies where IPLA was used. Some evidence indicate IPLA may significantly reduce the consumption of opioid[19]. Acetaminophen will be administered orally and overall consumption will be captured. 2) Peak expiratory flow (PEF), as measured by the incentive spirometry. PEF has not been studied in obese patients. There is no recommendation on a clinically significant change. 3) 6-min walk distance (6 MWD), defined as the distance (in meters) 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. Clinically significant differences occur at a minimum of 80m [26].

Pain scores will be measured at baseline, immediately in recovery, at 1, 2 and 4 hours post-operation and then every 4 hours for 24 hours, then every 8 hours up to a maximum of 48 hours post-operation. Opioid consumption will be measured immediately after the surgery, then at 1, 2, 4, 12, 24, and then 48 hours or sooner if patient is discharged earlier. PEF scores will be measured at baseline, immediately in recovery and then every four hours for a period of 24 hours, then every 8 hours up to a maximum of 24 hours post-surgery. 6

MWD will be measured at the baseline, on postoperative days one and two and at follow-up clinic within 10 days of operation.

Explanatory endpoint

Quality of life as measured by the QR-40 will be measured. It is a validated instrument that was developed specifically for post-operative patients [27].

QR-40 scores will be recorded at baseline, prior to discharge and at clinic follow-up within 10 days of discharge.

Study Flow

An overview of planned data collection is demonstrated in table 1.

Sample Size

There is relatively little information on the distribution of pain scores, health-related quality of life scores, or on recruitment and retention rates in the obese patient population. The main purpose of the proposed pilot trial is to define the distribution in outcome measures, as well as the feasibility of recruiting and retaining patients for a more definitive trial.

The sample size for pilot trials is typically determined pragmatically, with recommendations of 30-60 participants per arm. Based on a loss to follow-up of 10% with 95% CI of 12.7%-16.3%, we anticipate a recruitment rate of 33 to 38 patients per month to a total of 120 subjects within a four month recruitment period.

RESCUE MEDICATION AND RISK MANAGEMENT

The organization, monitoring, quality assurance will be under the responsibility of the principal investigator.

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Peak serum concentration of the Ropivacaine occurs 30 minutes after instillation [15] and decreases thereafter. Patients will receive standard cardiorespiratory monitoring, 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 to 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. 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.

DISCONTINUATION CRITERIA

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.

DATA SAFETY MONITORING

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 DSMD will perform ongoing review of safety and efficacy data to minimize exposure of patients to unsafe therapy or dose, make recommendations for changes in the study processes where appropriate, advise on the need for dose adjustment for safety issues, and endorse study continuation.

The sponsoring organization, the Ottawa Health Research Institute (OHRI) will also internally audit the trial conduct at the beginning and every 3 months during the trial.

DATA COLLECTION AND ANALYSIS PLAN

Research assistants will collect majority of the data and nurses on the bariatric floor will also help collect pain score and peak expiratory flow while patients are recovering in the bariatric unit. Nurse educator, nursing unit coordinator in the relevant hospital units have been informed and trained for the study. Research assistants have been trained by the sponsoring OHRI on accuracy and consistency of data collection.

The primary and secondary efficacy analysis will be based on the assigned treatment of patients (intention to treat analysis). Efficacy measures will be analysed using a mixed modelling approach to account for the dependence between measurements taken over time from the same patient. The comparison of the treatment arms for the efficacy endpoints will be conducted at a two-sided significance level of 0.05. Post-hoc pair wise comparison of the treatment arms at different time points will be done using multiple comparisons with adjustment to the type I error rate. No interim analysis is planned for this study.

QR-40 will be analysed by various cross-tabulations, confidence intervals and proper graphical displays. Parametric and non-parametric correlation coefficients scatter plots and box-whisker plots will be studied. Measurements over-time will be summarized at each interval. QR-40 over time will be compared between treatment arms.

Outcome assessors involved in the measuring and collecting of study endpoints will be blinded to the intervention.

The trial data will be housed on the OHRI network and will only be accessible to study investigators and research assistants upon request.

SAFETY

Safety endpoints are:

- Serious adverse event rates– defined as the fraction of subjects with an SAE.
- Surgical complications rates – defined as the fraction of subjects with a surgical complication

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. Serious adverse events are not anticipated in this study.

Safety analysis

The safety efficacy analysis will be based on the treated population. Subjects will be included in the analysis according to the treatment received.

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 preferred term and system organ class. Information regarding the occurrence of surgical complications events will be recorded on 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.

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).

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 for Ropivicaine. An unexpected event for a Ropivicaine 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 Ropivicaine, Health Canada will be notified within 7 calendar days.

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ETHICS AND DISSEMINATION

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has approved the study and all participants will be provided informed consent. All changes to the trial protocol are required to be approved by the OHSN-REB.

Only the study research assistants and individuals in the patient's circle of care will have access to patient information.

The study results will be made publically available through local, national, and international conferences, as well as peer-reviewed journals.

DISCUSSION

Outcomes of this pilot trial will determine the feasibility of a larger randomized controlled trial. Recruitment rates, logistics of randomization, treatment allocation, and data acquisition will all be used to assess the feasibility of the definitive study. ~~Evidence of~~ Improvement of ~~reduced~~ post-operative pain management offers great benefit to patient care and quality of life. It provides surgeons and anaesthesiologists with further opportunity to improve patient comfort and; reduce complications, reduce length of stay and healthcare costs. On the other hand, if our study finds evidence to indicate equivalence between IPLA and control arms in postoperative pain control, the already established use of Ropivicaine by many clinics in North America and Europe, would be challenged.

REFERENCES:

1 Fernandez AZ, Demaria EJ, Tichansky DS, *et al.* Multivariate Analysis of Risk Factors for Death Following Gastric Bypass for Treatment of Morbid Obesity. *Ann Surg* 2004;**239**:698–703. doi:10.1097/01.sla.0000124295.41578.ab

2 Narchi P, Benhamou D, Fernandez H. Intraperitoneal local anaesthetic for shoulder pain after day-case laparoscopy. *Lancet* 1991;**338**:1569–70. doi:10.1016/0140-6736(91)92384-E

3 Bisgaard T, Klarskov B, Kristiansen VB, *et al.* Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 1999;**89**:1017–24.http://www.ncbi.nlm.nih.gov/pubmed/10512282 (accessed 4 Oct2013).

4 El-Sherbiny W, Saber W, Askalany AN, *et al.* Effect of intra-abdominal instillation of lidocaine during minor laparoscopic procedures. *Int J Gynaecol Obstet* 2009;**106**:213–5. doi:10.1016/j.ijgo.2009.04.016

5 Kang H, Kim B-G. Intraperitoneal ropivacaine for effective pain relief after laparoscopic appendectomy: a prospective, randomized, double-blind, placebo-controlled study. *J Int Med Res*;**38**:821–32.http://www.ncbi.nlm.nih.gov/pubmed/20819419 (accessed 11 Oct2013).

6 Kahokehr A, Sammour T, Shoshtari KZ, *et al.* Intraperitoneal local anesthetic improves recovery after colon resection: a double-blinded randomized controlled trial. *Ann Surg* 2011;**254**:28–38. doi:10.1097/SLA.0b013e318221f0cf

7 Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. *Anesth Analg* 2006;**103**:682–8. doi:10.1213/01.ane.0000226268.06279.5a

8 Marks JL, Ata B, Tulandi T. Systematic review and metaanalysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. *J Minim Invasive Gynecol*;**19**:545–53. doi:10.1016/j.jmig.2012.04.002

9 Pappas-Gogos G, Tsimogiannis KE, Zikos N, *et al.* Preincisional and intraperitoneal ropivacaine plus normal saline infusion for postoperative pain relief after laparoscopic cholecystectomy: a randomized double-blind controlled trial. *Surg Endosc* 2008;**22**:2036–45. doi:10.1007/s00464-008-9762-x

10 Gupta A. Local anaesthesia for pain relief after laparoscopic cholecystectomy--a systematic review. *Best Pract Res Clin Anaesthesiol* 2005;**19**:275–92.http://www.ncbi.nlm.nih.gov/pubmed/15966498 (accessed 1 Oct2013).

11 Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. *Anesthesiology* 2006;**104**:835–46.http://www.ncbi.nlm.nih.gov/pubmed/16571981 (accessed 11 Oct2013).

12 Graf BM. The cardiotoxicity of local anesthetics: the place of ropivacaine. *Curr Top Med Chem* 2001;**1**:207–14.http://www.ncbi.nlm.nih.gov/pubmed/11895138 (accessed 11 Oct2013).

13 Knudsen K, Beckman Suurküla M, Blomberg S, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997;**78**:507–14.http://www.ncbi.nlm.nih.gov/pubmed/9175963 (accessed 11 Oct2013).

14 Callesen T, Hjort D, Mogensen T, *et al.* Combined field block and i.p. instillation of ropivacaine for pain management after laparoscopic sterilization. *Br J Anaesth* 1999;**82**:586–90.http://www.ncbi.nlm.nih.gov/pubmed/10472228 (accessed 11 Oct2013).

15 Labaille T, Mazoit JX, Paqueron X, *et al.* The clinical efficacy and pharmacokinetics of intraperitoneal ropivacaine for laparoscopic cholecystectomy. *Anesth Analg* 2002;**94**:100–5, table of contents.http://www.ncbi.nlm.nih.gov/pubmed/11772809 (accessed 4 Oct2013).

16 Kucuk C, Kadiogullari N, Canoler O, *et al.* A placebo-controlled comparison of bupivacaine and ropivacaine instillation for preventing postoperative pain after laparoscopic cholecystectomy. *Surg Today* 2007;**37**:396–400. doi:10.1007/s00595-006-3408-1

17 Park YH, Kang H, Woo YC, *et al.* The effect of intraperitoneal ropivacaine on pain after laparoscopic colectomy: a prospective randomized controlled trial. *J Surg Res* 2011;**171**:94–100. doi:10.1016/j.jss.2010.03.024

18 Cha SM, Kang H, Baek CW, *et al.* Peritrocal and intraperitoneal ropivacaine for laparoscopic cholecystectomy: a prospective, randomized, double-blind controlled trial. *J Surg Res* 2012;**175**:251–8. doi:10.1016/j.jss.2011.04.033

19 Symons JL, Kemmeter PR, Davis AT, *et al.* A double-blinded, prospective randomized controlled trial of intraperitoneal bupivacaine in laparoscopic Roux-en-Y gastric bypass. *J Am Coll Surg* 2007;**204**:392–8. doi:10.1016/j.jamcollsurg.2006.12.013

20 Alkhamesi NA, Kane JM, Guske PJ, *et al.* Intraperitoneal aerosolization of bupivacaine is a safe and effective method in controlling postoperative pain in laparoscopic Roux-en-Y gastric bypass. *J Pain Res* 2008;**1**:9–13.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3004614&tool=pmcentrez&rendertype=abstract (accessed 11 Oct2013).

21 Sherwinter DA, Ghaznavi AM, Spinner D, *et al.* Continuous infusion of intraperitoneal bupivacaine after laparoscopic surgery: a randomized controlled trial. *Obes Surg* 2008;**18**:1581–6. doi:10.1007/s11695-008-9628-2

22 Rodriguez L. Intraperitoneal analgesia compared with levobupivacaine 0.25% versus saline in laparoscopic bariatric surgery: 14AP5-11. *Eur J Anaesthesiol* 2011;**28**.

23 Betton D, Greib N, Schlotterbeck H, *et al.* The pharmacokinetics of ropivacaine after intraperitoneal administration: instillation versus nebulization. *Anesth Analg* 2010;**111**:1140–5. doi:10.1213/ANE.0b013e3181f3fb19

24 Maestroni U, Sortini D, Devito C, *et al.* A new method of preemptive analgesia in laparoscopic cholecystectomy. *Surg Endosc* 2002;**16**:1336–40. doi:10.1007/s00464-001-9181-8

25 Gallagher EJ, Bijur PE, Latimer C, *et al.* Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *Am J Emerg Med* 2002;**20**:287–90.http://www.ncbi.nlm.nih.gov/pubmed/12098173 (accessed 11 Oct2013).

26 Larsson UE, Reynisdottir S. The six-minute walk test in outpatients with obesity: reproducibility and known group validity. *Physiother Res Int* 2008;**13**:84–93. doi:10.1002/pri.398

27 Myles PS, Weitkamp B, Jones K, *et al.* Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth* 2000;**84**:11–5.http://www.ncbi.nlm.nih.gov/pubmed/10740540 (accessed 14 Oct2013).

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AUTHORS CONTRIBUTIONS

RW made contributions to study design, was involved in coordinating and overseeing the trial, and drafted the manuscript.

FH made substantial contributions to conception and design, was involved in coordinating the trial and writing and revising the manuscript.

NP and NE made substantial contributions to conception and design. They were involved in organizing the trial.

IR, JDY, AN were involved in organizing the trial. They were also involved in revising the manuscript.

TR made significant contributions to study design and statistical analysis.

JM made contributions to study design, was involved in overseeing the trial, revising the manuscript, and has given the final approval of the version to be published

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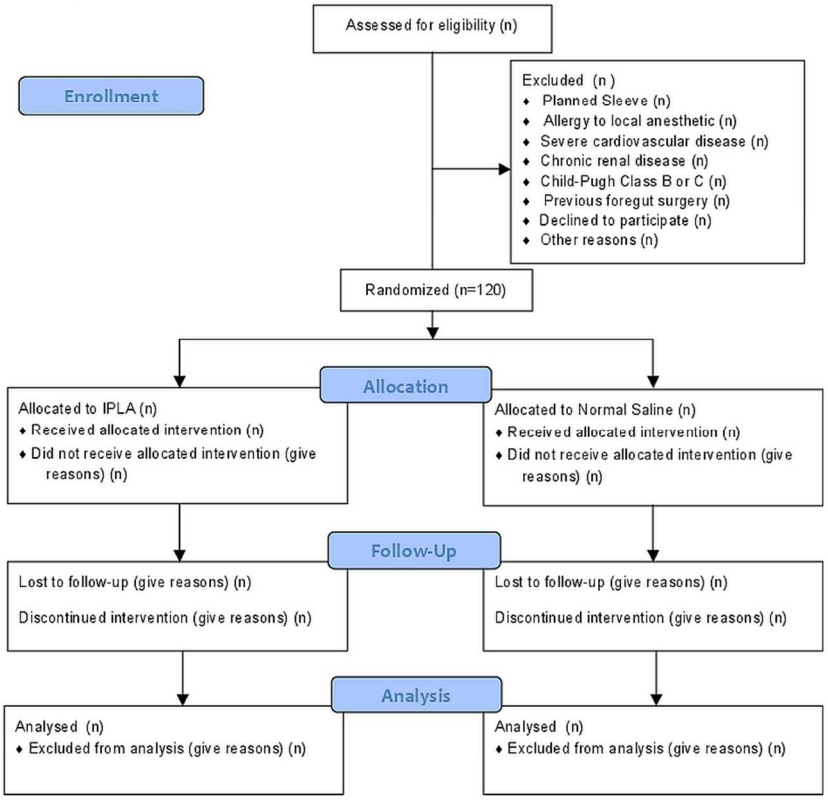
COMPETING INTEREST

The authors declare that they have no competing interests.

Acknowledgement

We thank Hadi Mehrzad Namazi for helping with the database creation of the study. We thank Dong Vo of the Ottawa Health Research Institute for creating the randomization scheme and database for the trial.

Figure 1. CONSORT Flow Diagram of the INOPAIN Study



Source: Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-91.

90x116mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	2
	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	15
	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)	11, 12N/A

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	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
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, noninferiority, 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	5
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)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	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)	11~~N/A~~
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	~~N/A~~7
	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	7-9
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)	10

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	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	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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	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 methods	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	~~N/A~~9 – VAS 10 – QoR Scale 12 – Data collection

	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	N/A – Patient data collection occur almost entirely during same stay
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	10
Statistical methods	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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	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)	12
Methods: Monitoring			
Data monitoring	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	12
	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	12~~N/A~~
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	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10

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)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A – no ancillary studies
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	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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	N/A – Patients are not considered to be more at risk than their baseline
Dissemination policy	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	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A – Full protocol will be available if this study is published

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	——————N/A – consent will be made according to institutional requirements
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 – No biological specimen will be collected

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.