PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Wu, Robert; Haggar, Fatima; Porte, N'Gai; Eipe, Naveen; Raiche, Isabelle; Neville, Amy; Yelle, Jean Dennis; Ramsay, Tim; Mamazza, Joseph

VERSION 1 - REVIEW

REVIEWER	Andrew Hill University of Auckland New Zealand
REVIEW RETURNED	13-Jun-2014

GENERAL COMMENTS	I have only one question/comment-Why are you doing a RCT to prepare for a future RCT. You have powered this study appropriately and I see no reason why a bigger study will be required eventually.

REVIEWER	Nawar Alkhamesi Minimal Invasive General and Colorectal Surgeon Department of Surgery University of Westren Ontario Canada
REVIEW RETURNED	17-Jun-2014

GENERAL COMMENTS	Very interesting study to advance our knowledge in pain management and patient care. I would like to suggest the following points to aid in making this study and any future follow on studies more robust in answering the trial questions 1. In page 7, under the heading interventions, I would like to see the anesthetic protocol added to the study so we can understand if the protocol has any effect on intraoperative and postoperative pain response and management. 2. In the same section, it will be of great benefit if the authors describe the methods through which the opioid and any other breakthrough pain medications will be delivered. That will also help in our understanding of how consumption of these medications will be measured. 3. Also, it would be in the interest of the study if the authors can explain to us what will be the effect of suction / irrigation that will be carried out during the procedure (if there is any bleeding or leak of

	any GI content) on the volume of the local anesthetic delivered prior to their dissection 4. To enhance the strength of this study and the future trial, I recommend that the author measures the plasma level of ropivacaine postoperatively at least in 2 occasions if possible to assess the level of the drug absorption if any on the patient's general health. HOWEVER, if this information is available through other similar studies (Peritoneal absorption of ropivacaine) then the authors need to reference that without doing the measurement themselves. 5. One extra point in page 5, the authors need to add the word CONVERSION in the last line, so the statement will read intra-operative conversion to sleeve gastrectomy …. This is a well-designed study and I recommend it for publication when the above questions are answered.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1, Dr. Andrew Hill: Thank you for your comments.

I have only one question/comment-Why are you doing a RCT to prepare for a future RCT. You have powered this study appropriately and I see no reason why a bigger study will be required eventually.
• Ropivacaine has not been previously used on the bariatric population for gastric bypass surgery. The visual analog scale also has not been formally used as research outcome measure within the bariatric population in a trial, therefore the expected degree of change of participants and the variance of the pain effect are unknown. Therefore we are at this point unable to accurately predict the sample size. The pilot study will help us obtain these measures to help with accurate sample size calculation.
• For assessment of the study process, we would like to understand the retention and follow-up rates of participants as they move through the trial. These measures are better assessed during a pilot study.

Reviewer 2, Dr. Nawar Alkhamesi: Thank you for your comments.

In page 7, under the heading interventions, I would like to see the anesthetic protocol added to the study so we can understand if the protocol has any effect on intraoperative and postoperative pain response and management.
• This has been added to the revised manuscript. The protocol has been standardized through meetings with involved anesthesiologists. Only short-acting agents may be used during surgery. Specifically, propofol or ketamine will be used for sedation, rocuronium or succinylcholine will be used for muscular blockade. Maintenance of general anesthesia will be achieved with dexmedetomidine and fentanyl boluses.

2. In the same section, it will be of great benefit if the authors describe the methods through which the opioid and any other breakthrough pain medications will be delivered. That will also help in our understanding of how consumption of these medications will be measured.
• As a secondary outcome, postoperative breakthrough medications will be captured with respect to quantity and route of delivery. The opioid dosage will be converted to standard morphine equivalent for comparison purposes. Acetaminophen use will be captured
• Our manuscript has been edited to further clarify this point.

3. Also, it would be in the interest of the study if the authors can explain to us what will be the effect of suction / irrigation that will be carried out during the procedure (if there is any bleeding or leak of any

GI content) on the volume of the local anesthetic delivered prior to their dissection
• Studies have shown that the peak concentration of Ropivacaine in an intra-peritoneal environment is achieved approximately 30 min after introduction. Ropivacaine has a very high absorption constant and is rapidly taken up systemically, the effect of irrigation and suction likely won't grossly impact the absorption of Ropivacaine unless the fluid is suctioned very quickly following its instillation. There are ample research support for the pre-emptive delivery of anesthetic prior to dissection, especially in the case of laparoscopic cholecystectomy. In these studies, the effect of intraperitoneal anesthetic is still evident despite not controlling for the irrigation and suction.

4. To enhance the strength of this study and the future trial, I recommend that the author measures the plasma level of ropivacaine postoperatively at least in 2 occasions if possible to assess the level of the drug absorption if any on the patient's general health. HOWEVER, if this information is available through other similar studies (Peritoneal absorption of ropivacaine) then the authors need to reference that without doing the measurement themselves.
• The systemic absorption of ropivacaine through peritoneal approach has been studied previously and peak plasma concentration was found to be much less (1.14 ug/ml) than the maximum tolerable level of 2.2 mg/L.
• Reference was provided in the updated manuscript.

5. One extra point in page 5, the authors need to add the word CONVERSION in the last line, so the statement will read intra-operative conversion to sleeve gastrectomy ….
• This has been corrected on the edited version.