PROTOCOL

SOOThe: **S**tudy of **O**besity-reduction and **O**piate-free **T**IVA

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Author/s:
Douglas Hacking, Justin Nazarath, Ranj Guha, Daniel Banyasz & Kit James

Sponsor/s:
Anaesthesia Department of Austin Health

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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STUDY SYNOPSIS (please provide a brief information)

Title:	**SOOThe**: **S**tudy of **O**besity-reduction and **O**piate-free **T**IVA
Short Title:	**O**besity-reduction and **O**piate-free **T**IVA
Design:	Randomised Controlled Trial
Study Centres:	Austin Health
Hospital:	Surgery Centre Heidelberg Repatriation Hospital & Austin Hospital
Study Question:	Does Opiate Free TIVA improve post operative recovery in bariatric patients undergoing laparoscopic surgery?
Study Objectives:	Assessment of post operative pain, post operative Nausea and vomiting (PONV) & rehabilitation
Primary Objectives:	Pain scores, Incidence of PONV, duration of ileus and time to discharge
Secondary Objectives	[1] Total Opiate use in Post Anaesthesia Care Unit (PACU) and the post operative ward [2] Dispensation of additional anti-emetic medication in PACU and post-operative ward
Inclusion Criteria:	Elective, cognisant, adult patients booked for gastric reduction surgery

Exclusion Criteria:	[1] Patients with a history of chronic pain [2] Patients with a history of dementia or cognitive impairment [3] Patients that do not wish to consent to the study [4] Patients with a history of significant allergy or anaphylaxis to Ketamine, Propofol, Opiates and lignocaine [5] Patients who are under 16 years of age or who are above 80 years of age [6] Patients who plan not to be an inpatient for 48 hours following surgery [7] Patients with a significant history of ischaemic heart disease (IHD) who have existing arrhythmias, low left or right ejection fraction (below 40%) or raised pulmonary blood pressure [8] Patients already prescribed sodium channel blockers as part of the management of pre-existing IHD [9] Pregnancy
Number of Planned Subjects:	130
Investigational product:	TIVA (Propofol, Lignocaine, Dexmedetomidine, Ketamine)
Safety considerations:	None in addition to safe anaesthesia in Bariatric patients. We seek to investigate a combination of Anaesthetic agents that are in standard use for General Surgery in the context of Bariatric Surgery
Statistical Methods:	All analyses will be performed using the statistical software package STATA (Stata 2017). Paired t-test (for normally distributed data) or the Wilcoxon signed ranks test (for non-normally distributed data) will be used to determine statistical significance in the change of Pain Scores and physiological parameters.
Subgroups:	None planned

1. Glossary of Abbreviations & Terms

Abbreviation	Description (using lay language)
BMI	Body Mass Index
Cpt	Target Plasma Concentration
HDU	High Dependancy Units
IBW	Ideal Body Weight
ICU	Intensive Care Unit
OSA	Obstructive Sleep Apnoea
PACU	Post Anaesthesia Care Unit
PONV	Post Operative Nausea and Vomiting
QoR-40	Quality of Recovery 40 item Score
TCI	Target Controlled Infusion
TIVA	Total Intravenous Anaesthesia
WHO	World Health Organisation
BASIG	Bariatric Anaesthesia Special Interest Group

2. Study Sites

a. Study Location/s

Site	Address	Contact Person	Phone	Email
Austin Hospital	Studley Road, Heidelberg, VIC 3084	Douglas Hacking	0419 629 041	Doug.HACKING@austin.org.au
Heidelberg Repatriation Hospital	300 Waterdale Road, Heidelberg Heights, VIC 3018	Douglas Hacking	0419 629 041	Doug.HACKING@austin.org.au

3. INTRODUCTION/BACKGROUND INFORMATION

a. LAY SUMMARY

Excess weight gain is a major problem in both the developed and the developing world as it is associated with a number of diseases such as heart attacks, strokes, diabetes, back pain, the need for early joint replacements and cancer. These significant health problems when taken together cause early disability and death. Studies have shown that treatment with both medicines and surgery leads to the best outcomes in terms of sustained weight loss and the prevention of diseases associated with being overweight. The problem is that being very overweight increases your risk when having surgery. Larger patients have more sickness after surgery and are prone to severe snoring which may prevent normal breathing. There is some evidence that avoiding strong pain killers (known as opiates such as morphine) through the use of local anaesthetic given in the vein (intravenous lignocaine) may be better for patients with weight problems as they have no more pain, less sickness and recover sooner In addition giving an anaesthetic solely through the vein (**T**otal **I**ntra**V**enous **A**naesthesia or TIVA) and avoiding inhaled anaesthesia otherwise (known as volatile anaesthesia) may also reduce sickness in the post operative period. Sadly there are not many studies on TIVA and it is not clear what the best recipe for this type of anaesthetic maybe in patients with weight problems. We think that using continuous carefully monitored infusions of four drugs together (Dexmedetomidine, Ketamine, Lignocaine and Propofol) without strong pain killers like opiates may be better for pain, sickness and post operative healing. This study is the first part of the process to see if TIVA without strong pain killers is better in overweight patients.

b. INTRODUCTION

Obesity is a major public health problem in both the developed and the developing world. A therapeutic approach that includes both bariatric surgery and medical management is more effective than medical management alone. However, bariatric patients are more prone to post operative complications that include post operative nausea and vomiting (PONV) and obstructive sleep apnea (OSA) both of which are caused by opiate administration. Despite the potential for both total intravenous anaesthesia (TIVA) and lignocaine infusions to reduce both of these morbidities there are few published reports in the literature on their use in bariatric patients. We propose to perform a pilot study in which patients are randomised to opiate free TIVA (Dexmedetomidine, Ketamine, Lignocaine and Propofol) or standard volatile-opiate based general anaesthesia and post operative care. We postulate that opiate free TIVA will provide ***improved*** analgesia, reduce PONV, cause less respiratory adverse events and lead to better post surgical rehabilitation. Ultimately we seek to establish a program of research which assesses the best method of Anaesthesia in Bariatric Patients. Pilot data will be used in grant applications to the Australian and New Zealand College of Anaesthetists (ANZCA) and the National Health and Medical Research Council (NHMRC).

c. Background information

Obesity is one of the most significant heath challenges affecting both developed and developing world countries (1). The incidence of obesity is rising rapidly across high-income countries, with the current prevalence in the USA (36 per cent) and UK (26 per cent) expected to double by 2050 (2). Moreover, lower income countries that have adopted western lifestyles have seen a similar rise in obesity with the incidence of this condition tripling in the last 20 years (3).

Table 1. World Health Organisation Obesity

Body mass index; kg.m^2	Classification
< 18.5	Underweight
18.5–24.9	Normal
25.0–29.9	Overweight
30.0–34.9	Obese 1
35.0–39.9	Obese 2
> 40.0	Obese 3 (previously 'morbid obesity')

Traditional classifications of obesity is defined as a body mass index (BMI) of greater than 30kg per meter square whilst those with a BMI above 35 are classified as morbidly obese and those with a BMI above 55 are termed super morbidly obese. World Health Organisation (WHO) classifications have since refined these categories (Table 1) into Obese 1 (BMI >30), Obese 2 (BMI >35) and Obese 3 (BMI >40) (4).

Obese patients are more likely to present to hospital as obesity is associated with a number of significant co-morbidities which include hypertension, coronary artery disease, sudden cardiac death, restrictive lung disease, obstructive sleep apnea (OSA), degenerative joint disease, diabetes mellitus, gallstones, obstruction in labour and an increase in the incidence of cancers of the breast and gasto-intestinal system as well as gynaecological malignancies. In addition to these medical factors which reduce life expectancy obesity has a significant effect on quality of life by increasing socioeconomic and psychosocial impairment (5). Not only are obese patients over represented within hospital populations they are more likely to be associated with post operative complications than those with a normal BMI (6-10). Furthermore they are more likely to require high resource care in terms of high dependancy units (HDU) and intensive care units (ICU) (11).

Of the healthcare interventions available to treat Obesity there is significant evidence that a combination of medical therapy and surgical intervention yields greater success in treating the complications of obesity than medical therapy alone (12). Moreover, follow up studies show that the benefits of bariatric surgery persist in the long term (13-15).

The imperative to develop safe and effective anaesthetic strategies for bariatric surgery is high given the risks of surgery in the obese and the efficacy of bariatric surgery in preventing severe long term morbidity. However, traditional volatile anaesthesia with opiate based analgesia runs the risk of causing both post operative nausea and vomiting (PONV) and OSA.

Fortunately intravenous Lignocaine may be a potent therapy within bariatric anaesthesia as it has been shown to reduce pain both to open and laparoscopic surgery, decrease PONV and the lessen the incidence of post operative ileus (16). Many of these benefits could be a result of reduced opiate consumption (16,17). However, there is increased interest in the effects of lignocaine which extend beyond sodium channel blockade. For instance the analgesic action of this drug extends well beyond the half life of the molecule (18) suggesting that anti-inflammatory effects of lignocaine, which include blockade of neutrophils (19), maybe just as important as its analgesic properties. These anti-inflammatory properties would be particularly important in obesity where inflammation is a significant part of the pathogenesis of its associated co-morbidities (20, 21).

Existing research on Total Intravenous anaesthesia (TIVA) and lignocaine in Bariatric patients

Despite the promise of intravenous lignocaine and total intravenous anaesthesia (TIVA) there is a scarcity of data in the public domain on its use within bariatric anaesthesia.

Ziemann-Gimmel and co-workers published a small study of 119 patients randomised to either traditional volatile and opiate anaesthesia or opiate-free TIVA using Propofol, Ketamine and Dexmedetomidine (22). They showed a reduction in severe PONV but not in mild or moderate PONV. They did not show any difference in the consumption of antiemetic medication. However, they measured PONV at a single time point so may have missed the true incidence of PONV. This is the only study to date to examine Dexmedetomidine in the context of bariatric surgery. Dexmedetomidine was once an expensive drug whose economic case was made in ICU based on a shorter time to extubation. Since the cost of this drug has fallen there is merit in examining its efficacy in a general surgical setting alongside other agents such as Lignocaine (23).

De Oliveira and colleagues (17) conducted a small (50 patient) randomised double blinded placebo controlled trial of intra-operative lignocaine against saline in laparoscopic gastric reduction surgery. They found that patients who had received intra-operative lignocaine had less pain and discomfort as assessed by the Quality of Recovery 40 item (QoR-40) questionnaire at 24 hours. Moreover, the lignocaine group had less opiate consumption both in PACU and on the post operative ward. Nausea but not vomiting in PACU was reduced in the lignocaine group. The small size of the study prevented assessment of whether lignocaine affected individual components of the QoR-40 score. The study did not go on to assess whether lignocaine improved long term rehabilitation from surgery.

There have been no studies to demonstrate a reduction in adverse respiratory events such as hypoventilation and hypoxia with bariatric anaesthetic technique. There have been no studies looking at the combination of Dexmedetomidine & Lignocaine together.

4. Study Objectives

a. Hypothesis

This pilot study starts to explore the extent to which Opiate-free TIVA improves post operative outcomes following bariatric surgery in obese patients. We hypothesise that in the first 48 hours of the post operative recovery time Opiate free TIVA when compared to standard care, in the form of Opiate based Volatile Anaesthesia, would:

[1] Provide either equivalent or improved analgesia

[2] Be associated with less PONV

[3] Lead to earlier acute rehabilitation

b. Study Aims

For the first 48 hours of the post operative recovery period in patients randomised to either Opiate free TIVA or standard care, Opiate based Volatile anaesthesia we will:

[1.1] Measure their pain scores using the QoR-40 questionnaire in PACU and on Days 1 and 2

[1.2] Quantify the total opiate dose used in PACU and on Days 1 and 2

[2.1] Measure the degree of nausea, vomiting and retching using the QoR-40 questionnaire

[2.2] Quantify the total anti-emetic dose used in PACU and on Days 1 and 2

[3] Measure the time to taken to reach acute rehabilitation through time to flatus, time to defecation and time to discharge

c. Outcome Measures

[1] The primary outcome measure is the post operative pain measured by analgesic requirement in PACU, Day 1 and Day 2 after surgery

[2] The secondary endpoints are:

[2.1] Post operative pain as measured by the QoR-40 pain score in PACU, Day 1 and Day 2 after surgery

[2.2] PONV as measured by the prescription of additional anti-emetic doses used in PACU, Day 1 and Day 2 after surgery

[2.3] PONV as measured by the QoR-40 questionnaire in PACU, Day 1 and Day 2 after surgery

[2.4] The time taken to reach acute rehabilitation as measured by the QoR-40 questionnaire in PACU, Day 1 and Day 2 after surgery

5. STUDY DESIGN

a. STUDY TYPE & DESIGN & SCHEDULE

Study Type

This will based in two hospitals (Austin Hospital & Repatriation Hospital) within a single-healthcare centre (Austin Health). The study is designed as a double blinded randomised control study in adult (>18 years) patients undergoing laparoscopic bariatric general surgery involving informed consent. Recruitment methodology is described in Section 6.a. and inclusion and exclusion criteria are described in Section 6.b. and 6.c.

Patient Risk Factors

This patient group's main risk factor is metabolic syndrome from morbid obesity. For this population Type 2 Diabetes Mellitus, hypertension and hypercholesterolaemia are common. . However, despite these co-morbidities the population represents a low to moderate operative risk because they are will have been managed in the endocrine clinic for at least 6 months before and have demonstrated significant weight loss on diet alone. These patients tend to be young and the timing of the bariatric surgery is designed to occur prior to significant systemic pathology such as ischaemic heart disease and peripheral vascular disease.

Intervention

The patients will be identified in the Bariatric Clinic prior to surgery and if they are willing to be part of the study randomised to either Opiate Free TIVA anaesthesia or Opiate based volatile anaesthesia. Details of the General Anaesthetic Protocol is in Section 5 (d) Study Methodology. Both general anaesthetic methods are well established methods of care both in the literature and through routine practice within the Austin Bariatric Anaesthetic Special Interest Group (BASIG: Douglas Hacking, Justin Nazarath, Ranj Guha, Daniel Banyasz & Kit James).

At present there is equipoise both within the Austin BASIG and in the literature as a whole as to whether Opiate free TIVA is superior to conventional volatile opiate anaesthesia.

Since there has been a higher reported incidence of intra-operative awareness with TIVA [24] all patients will receive Sedline Brain function monitoring intra-operatively as well as EEG monitoring. In addition Patients will be screened for awareness during general anaesthesia (AAGA).

Blinding

The patient will not be informed as to the type of anaesthetic they receive. However, Anaesthetist will not be blinded to the method of anaesthesia and will note down the total drug doses given during the procedure. The Post Anaesthesia Care Unit (PACU) staff will be blinded as to the anaesthetic given perform the first assessment of pain, PONV and acute rehabilitation using the QoR-40 questionnaire. The PACU staff will also note the type and total of analgesic and anti-emetic medication given. These assessments of pain, PONV and Rehabilitation, with totals of analgesic and anti-emetic medication will be repeated daily on the post operative surgical ward by Surgical interns who will also be blinded as to the type of anaesthetic. Further details of the randomisation process will be give under section 5c.

Data Collection

The data collected are listed the Study Table below. The following sources of data are noted:

- Patient demographic, screening details
    - This will be obtained from the medical record and from direct patient questioning if required. This data will be identifiable.
- Patient co-morbidities, surgical details:
    - This will be obtained from the medical record. This data will be re-identifiable.

QoR-40 data on Pain, PONV and Acute rehabilitation will be taken at three times during the inpatient stay (PACU, Day 1 and Day 2) and will take no more than 5 minutes to complete on each occasion. This study will therefore not be a major imposition on the patients during their post operative recovery. Total drug doses will be obtained from the medical record.

Screening data will be collected on a paper Case Report Form (CRF) that has identifiable data to enable cross-referencing and for future data clean up and to record randomisation strategy. All patients will then be assigned a unique number. All subsequent data will be collected on another paper CRF (the data CRF) that will only have a unique number to identify patients. The screening paper CRF will be kept securely in a locked office in a locked cabinet that is physically separate to the data CRF that will also be kept in a locked office in a locked cabinet within the Department of Anaesthesia. All data will be analysed. presented and/or published in a non-identifiable format. De-identified data will then be transcribed to an electronic spreadsheet (i.e. Microsoft Excel) which will be password protected.

The time frame is envisaged to be 1 year. Apart from the time required for screening and consent, all other patient data will be collected intra-operatively during the first 48 hours of the post operative period.

Contingency plans include the inclusion of 5 lead investigators to accommodate brief absences and to ensure integrity of access to research database.

No Biological samples or additional radiological investigations will be collected beyond those required for standard routine care. No new devices will be used in the course of this study. There will not be requirement for home visits or long term follow up. That said patients involved in the study can contact the researchers at any stage.

Study Table

Assessment/ Procedure	Visit 1	Visit 2	Intra-operative Intervention	PACU Post Operative Follow Up	Day 1 Post Operative Follow Up	Day 2 Post Operative Follow Up
Screening, Informed Consent	**x**					
Demographic Information, comorbidities,	**x**					
Randomisation, confirmation of consent		**x**				
Data on type of Anaesthesia given data			**x**			
Data on total drug doses of infusions if used			**x**			
QoR-40 data Post Operative Pain				**x**	**x**	**x**
QoR-40 data on PONV				**x**	**x**	**x**
QoR-40 data on acute rehabilitation				**x**	**x**	**x**

b. Standard Care and Additional to Standard Care Procedures

Standard Care Procedures		
Procedure	**Time/Visit**	**Dosage/ Volume**
Haemodynamic Data	During Anaesthesia & Surgery	N/A
Depth of Anaesthesia Monitoring	During Anaesthesia & Surgery	N/A
Prevention of PONV	Anti-emetics during Anaesthesia and on the Post Operative ward	Dexamethasone (8mg), Droperidol (0.6mg) and Ondansetron (4mg)

Additional To Standard Care		
Procedure	**Time/ Visit**	**Dosage/Volume**
Opiate Free TIVA	During Anaesthesia & Surgery	Dexmedetomidine, (0.5mcg/kg/hour), Ketamine (0.15mg/kg/hour), Lignocaine (2mg/kg/hour)
QoR-40 data Post Operative Pain & PONV	PACU & Post operative ward	N/A

c. Randomisation

Group allocation will be determined by block randomization sequence generated by a web-based computer random sequence generator (https://www.sealedenvelope.com) in blocks of four with a 1:1 allocation ratio. Group allocation will be placed in an opaque, sealed envelope that is sequentially numbered by an independent party who will not be collecting or analyzing data. This numbered envelop will be given to the clinical Anaesthetist after informed consent and the envelop will be opened prior to induction. Data will be collected during the operation but group allocation will not be recorded on data CRF. This data will be analysed without group allocation known.

d. Study methodology

Study Population and General Anaesthetic Protocol

We aim to recruit 130 eligible and consented patients to be part of this study. Patients will be randomised to either Opiate Free TIVA or Volatile and Opiate General Anaesthetic Study Group.

[1] Opiate-Free TIVA General Anaesthesia Study Group :

[1.1] Induction: Dexmedetomidine (0.5mcg/kg over 10 minutes) Ketamine (0.5mg/kg), Lignocaine (1.0mg/kg (to a maximum of 200mg)) Propofol (Marsh TCI Cpt 4mcg/ml) and Vecuronium (0.1mg/kg).

[1.2] Maintenance: Dexmedetomidine (0.5mcg/kg/hour), Ketamine (3mcg/kg/minute) and Lignocaine (1mg/kg/hour, to a maximum of 200mg/hour).

[1.3] Addition multimodal analgesia will include Parecoxib 40mg and Paracetamol (IV, 1mg). Pantoprazole (40mg) intravenous will be given to reduce pain from gastro-oesphageal reflux.

[1.4] Dexamethasone (0.2mg/kg to a maximum of 8mg), Droperidol (10mcg/kg, to a maximum of 600mcg) and Ondansetron (0.15mg/kg to a maximum of 4mg) will be administered intra-operatively.

[1.5] Application of Bupivacaine to the surgical port sites by the surgeons

[1.6] Reversal with Sugamaddex 200mg

[1.7] Standard PACU protocols for Oxycodone (1mg, 2 minutely to a maximum of 10mg) will be prescribed and titrated to pain by PACU Staff.

[1.8] Regular ondansetron (4mg every 8 hours) will be prescribed for the first 48 hours after surgery. Breakthrough anti-emetics of Metoclopramide 0.2mg/kg will be used.

[2] Volatile and Opiate General Anaesthesia Study Group:

[2.1] Induction: Alfentanil 1mg, Propofol (4mg/kg), Desflurane (1 Minimum Alveolar Concentration, MAC) and Vecuronium (0.1mg/kg).

[2.2] Maintenance: Desflurane 1 MAC, Oxycodone (0.1mg/kg to a maximum of 10mg)

[2.3] Addition multimodal analgesia will include Parecoxib 40mg, Paracetamol (IV, 1mg). Pantoprazole (40mg) intravenous will be given to reduce pain from gastro-oesphageal reflux.

[2.4] Dexamethasone (0.2mg/kg to a maximum of 8mg), Droperidol (10mcg/kg, to a maximum of 600mcg) and Ondansetron (0.15mg/kg to a maximum of 4mg) will be administered intra-operatively. .

[2.5] Application of Bupivacaine to the surgical port sites by the surgeons.

[2.6] Reversal with Sugamaddex 200mg.

[2.7] Standard PACU protocols for Oxycodone (1mg, 2minutely to a maximum of 10mg) will be prescribed and titrated to pain by PACU Staff.

[2.8] Regular ondansetron (4mg every 8 hours) will be prescribed for the first 48 hours after surgery. Breakthrough anti-emetics of Metoclopramide 0.2mg/kg will be used.

[3] Post Operative Monitoring:

[3.1] Whilst TIVA patients cannot be blinded to intra-operative staff neither the PACU Staff, Ward Staff or Acute Pain Team will know to which arm (Opiate free TIVA General Anaesthesia or Volatile General Anaesthesia) the patient has been allocated.

[3.2] The Total Opiate dose in PACU will be noted.

[3.3] Daily doses of oral Oxycodone (Endone) will be assessed.

[3.4] The patients will be interviewed in PACU, daily for 48 hours on the post operative ward assessing for pain and discomfort using the QoR-40 questionnaire.

[3.5] The patients will be interviewed in PACU, daily for 48 hours on the post operative ward assessing for PONV using a four point rating scale (None, Mild, Moderate and Severe) as well as for the occurrence of retching and vomiting.

[3.6] Measures of acute rehabilitation will be assessed through questioning the time to first flatus, defecation and duration of hospital discharge.

Primary and Secondary outcomes (as above for Outcome Measures)

[1] The primary outcome measure is the post operative pain measured by analgesic requirement in PACU, Day 1 and Day 2 after surgery

[2] The secondary endpoints are:

[2.1] Post operative pain as measured by the QoR-40 pain score in PACU, Day 1 and Day 2 after surgery

[2.2] PONV as measured by the prescription of additional anti-emetic doses used in PACU, Day 1 and Day 2 after surgery

[2.3] PONV as measured by the QoR-40 questionnaire in PACU, Day 1 and Day 2 after surgery

[2.4] The time taken to reach acute rehabilitation as measured by the QoR-40 questionnaire in PACU, Day 1 and Day 2 after surgery

6. STUDY POPULATION

a. RECRUITMENT PROCEDURE

Eligible patients will be screened and identified by the research personnel when they attend pre-admission clinic for their upcoming general surgery or when the theatre booking is confirmed. Patients who are known to have English proficiency issues (e.g. those from a non-English speaking background) or who are known to have cognitive issues will not be recruited as the inability to provide informed consent is an exclusion criterion. The approach will then take place in person by the research personnel and is typically days or weeks in advance of surgery. If the approach is successful, a Participant Information and Consent Form (PICF) will be provided in person or via postal service / electronic mail. The time that a potential participant has to consider participation before consenting will therefore typically be days to weeks after being approached by research personnel. There are no differences between patients being recruited to either arms of this randomised controlled study.

b. Inclusion Criteria

Elective, cognisant, adult patients booked for elective gastric reduction surgery

c. Exclusion Criteria

[1] Patients with a history of chronic pain

[2] Patients with a history of dementia or cognitive impairment

[3] Patients that do not wish to consent to the study

[4] Patients with a history of significant allergy or anaphylaxis to Ketamine, Propofol, Opiates and lignocaine

[5] Patients who are under 16 years of age or who are above 80 years of age

[6] Patients who plan not to be an inpatient for 48 hours following surgery

[7] Patients with a significant history of ischaemic heart disease (IHD) who have existing arrhythmias, low left or right ejection fraction (below 40%) or raised pulmonary blood pressure

[8] Patients already prescribed sodium channel blockers as part of the management of pre-existing IHD

[9] Pregnancy

d. Consent

Participants will have already been initially approached by the research personnel at the earliest opportunity and subsequently given a PICF to peruse. Participants will typically have had days to weeks to consider participating in the research prior to consent being requested. An opportunity to ask questions about the research project or the PICF will be given to the participant prior to consent being obtained. Additionally, the research personnel will make an assessment as to the capacity of the participant to provide consent and understand instructions, which forms part of their professional conduct. Patients from a non-English speaking background (NESB) are unlikely to be recruited unless they demonstrate capacity to consent and understand instructions as determined by research personnel. If all questions have been satisfactorily addressed (or there are no questions), and if the participant is deemed capable of providing consent, then consent will be obtained.

Consent will be confirmed prior to randomisation. Consent will require a participant's signature to be witnessed. Please refer to PICF for further details

7. Participant Safety and Withdrawal

a. Risk Management and Safety

In principle management risk relates to the conduct of surgery and anaesthesia in bariatric patients as described above in the section 3(c) Background Information and section 5(a) Patient Risk Factors. Both anaesthetic techniques are established in routine use within the BASIG so there is no additional risk above standard clinical care posed by the study.

There is the potential for PONV with Volatile Opiate General Anaesthesia which is mitigated with routine prescription of three anti-emetic drugs in theatre (Section 5d: Study Population and General Anaesthetic Protocol). Opiate-free TIVA runs the risk of awareness the risk of which will be minimised by TCI and Sedline Brain Function Monitoring [24].

b. Handling of Withdrawals

Patients may be withdrawn from the study at any time. Withdrawal will only be permitted for participant choice. All data from withdrawn patients will be discarded. If there is a protocol violation (e.g. patient receive the wrong randomisation strategy) their data will still be included in sub-analysis of the data, but not in the primary analysis.

c. Replacements

All withdrawn patients will be replaced as this is a physiological study with a small sample size.

8. Statistical Methods

a. Sample Size Estimation & Justification

The largest study published to date on Opiate free TIVA had 119 patients within it (22). The study described here, which seeks to recruit 130 patients, is a pilot study which will establish proof of the principle. This will produce preliminary data that will form the basis of subsequent grant funding to ANZCA and the NHMRC for larger studies with greater power to assess the real role of TIVA within Bariatric Anaesthesia. None the less informal sampling of Bariatric patients undergoing both Volatile Opiate General Anaesthesia and Opiate Free TIVA suggests that the latter require 50 to 25% less opiate in PACU. On that basis a 50% difference in opiate prescription using a two sample means test would require 60 patients in each group (Total 130 patients) given an alpha value of 0.05 and a power of 0.8 assuming a standard deviation of 1.0.

b. Power Calculations

Assuming a statistically significant two way threshold of 0.05, a power of 0.8 and a standard deviation of 1.0 two sample means tests calculate:

[]1 A sample size of 90 (total of 45 in each group) for a difference of 0.6 in opiate use in PACU

[2] A sample size of 106 (53 in each group) for a difference of 0.55 in opiate use in PACU

[3] A sample size of 128 (64 in each group) for a difference of 0.5 in opiate use in PACU.

c. Statistical Methods To Be Undertaken

All analyses will be performed using the statistical software package STATA (Stata 2017).

Continuous data will be described as normally distributed if they satisfy the Shapiro Wilk test. All continuous normally distribute data will be described as mean (+/- SD) and non-normally distributed data as median (interquartile range).

The primary and secondary outcomes will be analysed using paired t-test or Wilcoxon Signed Rank Test (depending on the distribution of normality). A two- sided alpha value of 5% is specified as significant.

9. Storage of Blood and Tissue Samples

a. Details of where samples will be stored, and the type of consent for future use of samples

There are no plans to take any biological samples other than those required for No further storage is required and no genetic testing will be used. No sample will be added to a biobank.

10. Data Security & Handling

a. Details of where records will be kept & How long will they be stored

The paper records will be kept in a locked office in a locked cabinet within the Department of Anaesthesia. Screening data CRF (which will be fully identifiable) will be kept physically separate from the data CRF (which is re-identifiable using a unique number assigned to each participant). All data will be transcribed to an electronic CRF (using Microsoft Excel) which has no identifiable information on it (but will have re-identifiable data through the use of the unique number assigned to each participant) which will be password protected.

All records will be kept for a minimum of 7 years post study closure.

b. Confidentiality and Security

Confidentiality of all study data will be maintained by the use of unique number in the data CRF and the electronic CRF. This unique number is assigned to each participant and will be used instead of the use of any identifiers. All electronic data will be password protected.

c. Ancillary data

No ancillary data will be stored.

11. REFERENCES

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