CONFIDENTIAL

RANDOMISED SINGLE BLINDED TRIAL OF SURGICALLY PLACED PRE-PERITONEAL VS ULTRASOUND PLACED RECTUS SHEATH CATHETERS POST LAPAROTOMY

Protocol No: 1.02
Version: 3
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SPONSOR
Nil

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Protocol Number: 1.02 Version 3

Protocol Title: Randomised single blinded trial of surgically placed pre-peritoneal vs ultrasound placed rectus sheath catheters post laraotomy

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STUDY ACKNOWLEDGMENT/CONFIDENTIALITY

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice[1] (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by Company Name or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results there from and both parties shall co-operate in this regard.

PRINCIPAL INVESTIGATOR – NAME AND TITLE **Signature:**

Date:

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ABBREVIATIONS AND DEFINITIONS OF TERMS (examples only – modify as appropriate)

AE	Adverse Event
BMI	Body Mass Index (weight in kg divided by height in m^2)
BO	Bowels Open
CTN	Clinical Trial Notification
ECG	Electrocardiogram
IEC	Independent Ethics Committee
IV	Intravenous
Hr	Hour
MBH	Mackay Base Hospital
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
®	Registered Product
ROP	Ropivacaine
SAE	Serious Adverse Event
SD	Standard Deviation
US	Ultrasound
UTI	Urinary Tract Infection
VAS	Visual analogue scale (Score of 1-10 for pain)
VTE	Venous Thromboembolism

1 Synopsis

Study Title:

Randomised single blinded trial of surgically placed pre-peritoneal vs ultrasound placed rectus sheath catheters post laparotomy

Protocol Number:

1.02

Indication:

Patient undergoing a laparotomy (Emergency and Elective) under the general surgical team

Study Drugs:

Testing technique, not drugs. Both arms will then receive 20mL 0.2% Ropivacaine infusion through these catheters every 4 hrs for 3 days.

No. Participants:

72 Patients

No. Centres:

1 Centre; Mackay Base Hospital

Study Duration:

Approximately 1 year

Objectives of the Study:

The goal of this project is to prove if surgically placed pre-peritoneal catheters are more effective than ultrasound placed rectus sheath catheters at improving post-operative pain.

Study Endpoints:

The primary endpoint is:

- Total narcotic usage until day 3 post op. This will be measured in mg of IV Morphine. All other narcotic agents (Oral or IV) will be calculated back to IV Morphine equivalence as per dosage equivalence on MIMs.

Secondary endpoints:

- Time taken for procedure (Minutes)
- Patient blinded VAS scores at rest and coughing (0-10)
- Time till flatus (Days)
- Time till BO (Days)
- Time till discharge (Days)
- Complications
    - Wound infection
    - UTI
    - VTE

Study Design:

All enrolled patient will be randomised into two even arms via random allocation sequence in numbered envelopes. A third party doctor using computer randomisation will conduct the randomisation prior to commencement of the project. The allocation will be revealed prior to closure of the abdomen where the patient will either receive a surgically placed pre-peritoneal catheter or an ultrasound guided rectus sheath catheter inserted by the anaesthetic team prior to waking up from the general anaesthetic.

These catheters will then be intermittently infused with local anaesthetic over the next 72 hours via a pump. Over this time the patients' opiate analgesic requirement and the visual analogue scale (VAS) will be monitored daily. The surgical team and the anaesthetic pain team will review the patients daily for the above and monitor for adverse effects from the procedure/local anaesthetic.

Eligibility Criteria (Inclusion and Exclusion)

Inclusion: All adult general surgical patients undergoing a midline laparotomy at Mackay base hospital

Exclusion Criteria:

- Local Anaesthetic allergy
- Catheter plastic allergy
- Multiple operations as defined as alteration of anatomy of the abdominal wall, preventing placement of catheters.
- Chronic abdominal pain as defined as abdominal pain with opiate use for > 12 weeks
- Abdomen left open
- Patient under 18 years of age
- Pregnant
- Inability of surgical/anaesthetic staff to perform procedure
- Patients with altered cognition (dementia or delirium) and therefore unable to respond to

VAS.

- Patients intubated & therefore unable to communicate

Sample Size Determination:

Calculation of the sample size was performed by using the primary endpoint of 72-hour total morphine usage post laparotomy. In a similar previous study, the total dose of administered morphine was 62mg with a standard deviation of 16mg.[4] It was decided that a difference of 20% (12mg) would be considered clinically relevant, similar to this previous study.

Assuming $\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}15$ (a power of 85 per cent), a total of 66 patients (33 patients per group) would be required to needed to find there was no difference between each group[10]. Assuming a 10% dropout rate 72 patients need to be recruited (36 patients per group) to make this number.

2 Introduction

Adequate postoperative analgesia post midline laparotomy has been associated with a decrease in cardiopulmonary complications, mortality, length of hospital stay and therefore a decrease in hospital costs.[1-2]

Opiate analgesic requirements post laparotomy are usually quite high and can have significant side effects such as respiratory depression, nausea, ileus, confusion and urinary retention.[2] To minimise opiate usage and therefore side effects a multimodal approach to pain with adjuvants such as Epidural or rectus sheath catheters are often used.[3]

Epidural analgesia, whilst being shown to be more effective than rectus sheath catheters in reducing post operative pain in most publications have numerous shortfalls.[2]They often don't have time to be placed in emergency laparotomies, have multiple contraindications and have rare, but clinically significant complications such as an epidural abscess or haematoma. They also require more monitoring post operatively and associated with significantly higher rates of hypotension post operatively.[2]

Whilst most studies have demonstrated efficacy of rectus sheath catheters, some older studies found no benefit compared with placebo. A recent systematic review and meta-analysis have shown that it does significantly decrease total opioid consumption.[5] Moreover, recent studies looking at more secondary endpoints have demonstrated a decreased time to recovery of bowel function, earlier mobilisation and decreased hospital stay when using rectus sheath catheters.[5,6,7]

Potentially the heterogeneity in the data in regards to of rectus sheath catheters in large is due to a wide variety of techniques used in their placement.[4]

In regards to safety of the rectus sheath catheters with continuous LA infusion, no studies have reported any significant complications.[5] Two small studies have been done looking for specific complications. The first was an observational, descriptive and prospective study of 50 patients which found that there was no increased incidence of wound infection with a rectus sheath catheter than without post lapraotomy.[9] The second study looked at blood levels, signs or symptoms of LA toxicity in 12 patients who had an U/S guided rectus sheath catheter placed.[8] The protocol of LA used involved a 20mL bolus of 0.5% ROP followed by 10 mL/h of 0.2% ROP infusion. It found that although the total plasma ROP concentrations just exceeded reported neurotoxicity thresholds, the unbound ROP concentration did not reach the toxicity threshold, and nil patients had any signs or symptoms of toxicity.[9]

It is standard practice for the placement of rectus sheath catheters following major abdominal surgery. A surgeon will insert the rectus sheath catheters prior to closure of the laparotomy incision abutting the transversalis fascia in the pre-peritoneal space. Alternatively an anaesthetist will insert the rectus catheters via US guidance into the rectus abdomini muscle. A detailed description of the technique used by both surgeons and anaesthetist in this study is included in section 7.4 of this protocol. Whilst in the literature both techniques of surgically placed pre-peritoneal catheters and US placed rectus sheath catheters have been found to be effective against placebo there have been no head to head trials to see if one is superior.

The only study directly comparing catheter placement was Khorgami et al.[4] They compared catheter placement in the rectus sheath (intrafascial) to the Subcutaneous (suprafascial) space. In this study it found that the intrafascial rectus sheath catheters were more effective in reducing morphine requirements, visual analogue scale (VAS) scores and time til BS returns than suprafascial catheters.

This study will be similar in nature to the aforementioned study[4] with the intention of finding whether a surgically placed pre-peritoneal catheter is a quicker, more effective option to the U/S placed

intrafascial rectus catheter. The other potential benefit theorised would be a decrease in visceral pain with a pre peritoneal catheter.

In this study, the catheters will be inserted and secured by either a surgical or anaesthetic consultant. Surgical consultants and anaesthetic consultants will be orientated to the standard specified procedure (as detailed in section 7.4 of this protocol) of placement as led by Dr C. F Pretorius (Director of Surgery) prior to the commencement of this study.

3 Objectives

Null hypothesis: Surgically placed pre-peritoneal catheters are superior to ultrasound placed rectus sheath catheters at reducing post-operative pain.

The primary endpoint is:

- Total narcotic usage until day three post op. This will be measured in mg of IV Morphine. All other narcotic agents (Oral or IV) will be calculated back to IV Morphine equivalence as per dosage equivalence on MIMs.

Secondary endpoints:

- Time taken for procedure (Minutes)
- Patient blinded VAS scores at rest and coughing (0-10)
- Time till flatus (Days)
- Time till BO (Days)
- Time till discharge (Days)
- Complications
    - Wound infection
    - UTI
    - VTE

4 Study Design

This will be a randomised, patient blinded trial. All enrolled patient will be randomised into 2 even arms – One to receive a surgically placed pre-peritoneal catheter, the other an ultrasound guided rectus sheath catheter inserted by the anaesthetic team prior to waking up from the general anaesthetic. Both will then receive 72 hours of intermittent Ropivacaine 0.2% boluses via these catheters.

Patients will be screened for the study when they are booked up for an emergency or elective procedure which will always or potentially require a midline laparotomy. These patients will then be consented for potential enrolment. Enrolment and allocation will be only revealed when it is sure that the patient does not meet any of the exclusion criteria in theatre prior to closure of the abdomen via randomised numbered envelopes.

These numbered envelopes will be generated prior to the start of the study by a 3rd party doctor. This doctor, who is not involved in the study in any other way, will use a random allocation sequence generated by computer using non-blocking randomisation.

Over the first 72hours the patients' opiate analgesic requirement, the visual analogue scale (VAS) and potential complications will be monitored daily by the surgical team and recorded on the data collection tool. During this time the anaesthetic team will also review the patient to monitor the local anaesthetic boluses are being administered correctly via the pumps and to look for adverse effects from the

procedure/local anaesthetic as well. After the 72 hours, unless to patient has ongoing pain issues, the surgical team alone will continue to see the patient daily and record any delayed complications until discharge.

This follow up, other than recording on the data collection sheet, is currently routine care for patients post laparotomy with rectus sheath catheters and will not significantly increase workload for the teams involved during the trial period.

5 Study Population

5.1 Number of participants

72 patients (36 patients per arm)

The following demographics and primary clinical characteristics which may cause a difference between the arms are outlined below. These will be record and analysed between the 2 arms to ensure there is nil significant bias.

Demographic factors
- Sex
- Age
- BMI
- ASA Score
- Creatnine

Primary clinical characteristics
- Procedure
- Procedure time
- Incision type (Full midline, upper midline, lower midline)
- Incision Length
- Stoma
- HDU/ICU Requirement
- Anaesthetic used

5.2 Inclusion Criteria

All adult general surgical patients undergoing a midline laparotomy

5.3 Exclusion Criteria

- Local Anaesthetic allergy
- Catheter plastic allergy
- Multiple operations as defined as alteration of anatomy of the abdominal wall, preventing placement of catheters.
- Chronic abdominal pain as defined as abdominal pain with opiate use lasting > 12 weeks
- Abdomen left open
- Patient under 18
- Pregnant
- Inability of surgical/anaesthetic staff to perform procedure
- Patients with altered cognition (dementia or delirium) and therefore unable to respond to VAS.
- Patients intubated & therefore unable to communicate

6 Study Assessments and Procedures

6.1 Screening Evaluation

Prior to commencement of this project, the surgical team (inclusive of RMO's, registrars and consultants) and anaesthetic team (RMO's, registrars and consultants) will be orientated to the consenting and recruitment process of this project. All patients to undergo a laparotomy at MBH by a general surgeon as either an elective or emergency procedure will be screened contiguously. They will be recruited once they meet inclusion criteria. At the time of consent to laparotomy, patients will be identified by the surgical registrar or consultant and will be recruited into the study if inclusion criteria are met. The "Poster" and "Recruitment Flowchart" will be printed and laminated and made available in every surgical outpatient and anaesthetic outpatient clinic room to serve as a strict guide to the recruitment process. These are attached. The investigators expect the majority of recruitment to occur in the outpatient setting. The " patient information sheet and consent forms" will be made readily available in the surgical department (ward, outpatient department and acute surgical unit). In regards to emergency surgery and recruitment, if it is deemed patient autonomy is compromised or if due to time constraints their specific concerns are not able to be addressed they will not be recruited in this study. If they meet exclusion criteria the 'Excluded patient data collection tool' is to be completed. If they do not meet exclusion criteria information about the study will be given to the patient and they will be asked to consent for potential enrolment as guided by the patient information sheet (as attached). A copy of the patient consent and recruitment agreement will be kept with the patient's consent to laparotomy. The investigators will enter patient information into a password secured database.

6.2 Study Procedures

6.2.1 Baseline (Day 0)

Data collection tool 'Patient Information' and 'Procedure' filled out by surgical registrar at the end of the procedure (Attached)

6.2.2 Day 1,2,3

Data collection will begin with documenting intraoperative analgesia & anaesthesia requirements. Subsequently data will collected on the premise of the VAS 12 hours post-operatively (at rest & at coughing) by the Surgical/Anaesthetic Registrar or Consultant. On the surgical ward round the registrar or consultant will ask whether the patient has opened bowel or passed flatus. All data will be recorded on the data collection tool, which will be placed in the patient's chart. The morphine equivalent analgesia can be, but does not have to be filled in. This can be retrospectively analysed for the patient med chart, chart notes, and anaesthetic pain round by the investigators. The investigators will be directly involved in reviewing each patient recruited in this study.

At any stage any complications can be written at the bottom of the Data collection tool.

6.2.1 Chart Follow up

Prior to completely de-identifying the patient, late complications will be assessed 2 months post op via a chart review.

	Procedure	Length of incision (cm)	Midline Incision (full/upper/lower)	Stoma (Y/N)	Anaesthetic used	Time taken for catheter (min)	Morphine equivalent analgesia (mg)	VAS Score at rest	VAS Score on coughing	Passed Flatus (Y/N)	Bowels Opened (Y/N)	Complications
Time of proceedure	X	X	X	X	X	X						X
Day 1 post op							X	X	X	X	X	X
Day 2 post op							X	X	X	X	X	X
Day 3 post op							X	X	X	X	X	X
Chart Review							X			X	X	X

Copies of the Data collection sheets are attached

6.3 Study Restrictions

6.3.1 Adverse Events

- Wound infection
- Haematoma
- Local anaesthetic toxicity

7 Investigational product(s)

7.1 Description of Investigational Product(s)

- 16G Portex® Extra length (110mm) Tuohy Needle
- 16G Epidural Catheter (Multiperforated with 3 lateral eyes)
- 16/17G LOCKIT PLUS™ Regional Anaesthesia Catheter Securement Device
- Alaris Products® 0.2µm Line Filters
- Opsite® Flexigrid (10x12cm)
- 20mL Luer-lock Syringe

See Figure 1 for a complete picture of all products used

Figure 1: Equipment used

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7.2 Dose Justification

Re: Ropivacaine HCl

TGA approved indications include field block (minor nerve block and infiltration) at a dose as below:
- Initial bolus: 2mg/Kg (For 0.2% (2mg/mL) 1mL/Kg)
- Ongoing infusion of Ropivacaine 0.2%: **10 – 20 mg/hr** (5 – 10 mL/hr) for up to 72 hours.

Study dose:
- 40mL initial infusion of Ropivicaine 0.2% (80mg)
- 20mL Ropivicaine 0.2% (80mg) every 4 hrs (40mg/4hrs = **10mg/hr** = 5mL/hr)

This is the current protocol at MBH. It is also at the lower range of the of the suggested infusion of Ropivacaine as to lower the small risk of local anaesthetic toxicity.

7.3 Comparator Justification

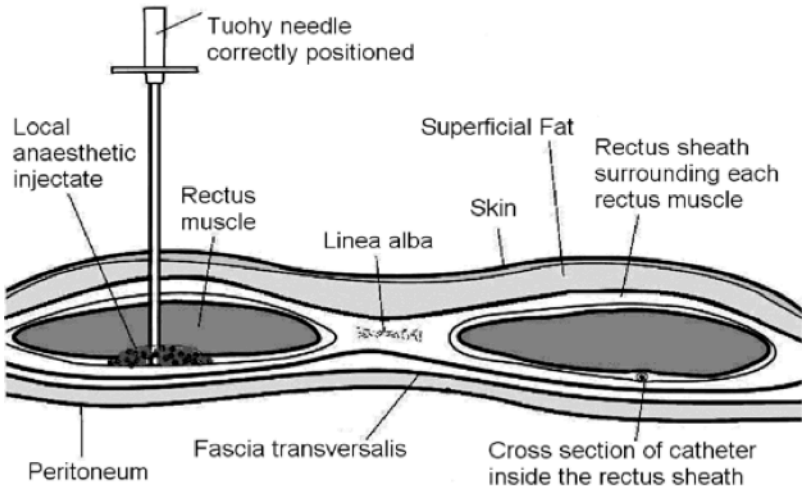
A recent systematic review and meta-analysis looking at both techniques together have shown that they both significantly decrease total opioid consumption compared to placebo.[5] Thus this study is not looking at equivalence to placebo, it is looking for the best technique head to head.

7.4 Techniques

Technique for Anaesthetically inserted rectus sheath catheter

1) The procedure takes place after abdominal wall closure, prior to dressings.
2) From the superior aspect of the incision a point 5-7cm lateral and 3cm cranial OR at the costal margin (If this former point is superior to the costal margin) is marked for the catheter insertion.
3) Under U/S guidance at this marking a 16G Tuohy Needle is inserted at approximately 30-45 Degrees in either a lateral to medial direction (To avoid epigastric arteries) or caudal direction or a combination.
4) When the tip of the needle is just below the rectus muscle before going though the posterior rectus sheath (Intrafascular space) some of the 20mL of 0.2% Ropivicaine is infused to hydro dissect and open up the space. See figure 2 for the correct placement
5) The angle of insertion is then dropped to parallel with the skin and the needle is advanced further.
6) The 16G Epidural Catheter is then inserted through the needle to approx. 10-15cm and the needle is withdrawn slowly to ensure the catheter does not move.
7) The Catheter is then secured with the Securement Device.
8) The catheter connecter, followed by the filter is then attached to the distal end of the catheter
9) The process is then repeated on the contralateral side.
10) The remainder of the 20mL of 0.2% Ropivicaine is infused on each side.

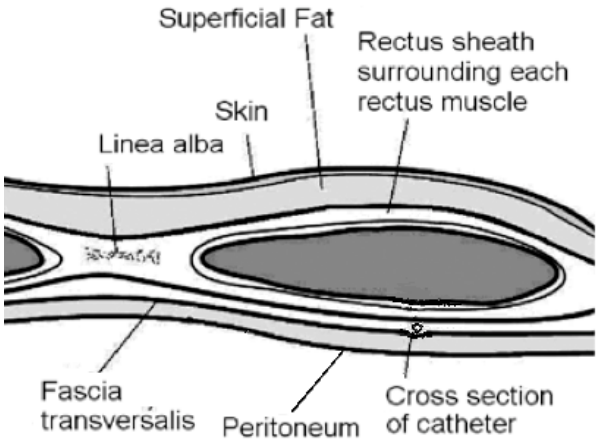
Figure 2: U/S placement location (Intrafasicular)



Technique for Surgically inserted rectus sheath catheter

1) The procedure takes place just prior to abdominal wall closure.
2) From the superior aspect of the incision a point 5cm lateral and 3cm cranial OR at the costal margin (If this former point is superior to the costal margin) is marked for the catheter insertion.
3) At this marking a 16G Tuohy Needle is inserted at approximately 45 Degrees in a caudal direction, parallel to the incision.
4) With the surgeon's other hand the inside the abdominal cavity, deep to the site of insertion, the needle is advanced until it has just passed through the rectus sheath and just lies in the pre-peritoneal plane.
5) The angle of insertion is then dropped to parallel with the skin and the needle is advanced further with the surgeon's other hand used to palpate the needle and ensure it remains in the correct plane.
6) The 16G Epidural Catheter is then inserted through the needle to approx. 10-15cm and the needle is withdrawn slowly to ensure the catheter does not move.
7) The Catheter is then secured with the Securement Device.
8) The catheter connecter, followed by the filter is then attached to the distal end of the catheter
9) The process is then repeated on the contralateral side.
10) 20mL of 0.2% Ropivicaine is infused on each side.
11) Once the wall closure has been completed a large transparent dressing is placed over the insertion site.

Figure 3: Surgical placement location (Pre-Peritoneal)



7.5 Randomisation Procedure

Randomisation will occur via a random allocation sequence which will be made by a third party (Dr Karen Pretorius) via computer randomisation prior to the project. There will be no restrictions such as blocking on this randomisation. The concealed sequence will be in ordered closed envelopes and only once the patient is enrolled will the arm they are allocated be revealed.

7.6 Unblinding Procedure

The patient can be unblended after all subjective testing is done on day 3 if they request.

8 Adverse Events (AE) and Serious Adverse Events (SAE)

The wellbeing and safety of participants in this research is the paramount. Although a recent systemic analysis has not linked this procedure to any adverse events (AE) or serious adverse events (SAE),[5] possible AE and their definition will be outlined below. Unexpected AE and SAE will also be monitored for and are defined below.

The investigators are responsible for the detection and documentation of AE or SAE as defined in this protocol. During the study, there will be a safety evaluation by the investigators in Mackay every month looking at AE. Any SAE is to be reported to the principal investigator within 24 hours. This will result in a safety evaluation of all current and past cases again and a report to the head of surgery and head of anaesthetics within 5 working days. Any time there is a SAE with definite or probable causality a report will be sent to the ethics committee and the trial may be suspended or terminated early at the principle investigator's, local head of department's or ethics committee's request.

8.1 Definition of an Adverse Event (AE) and a Serious Adverse Event (SAE)

Regarding the insertion/Catheter site:

- A simple abdominal wall haematoma (Bruise) will be recorded as AE. If it is associated with a Haemoglobin drop of >30 or requires a blood transfusion it will be recorded as a SAE and notified as above.
- Any damage to one of the intra-abdominal organs on insertion of the needle will be recorded as a SAE.
- A wound infection is defined by the treating team. This is because there is no standard laboratory test for defiantly deciding if a wound is infected or not, except clinically. This complication is common post laparotomy and will be monitored for up to 2 months post the procedure. If there is signs of wound infection prior to 72 hours the catheters must be withdrawn early and the reasons why clearly documented. If the infection results in a return to theatre or sepsis (As defined by SIRS) criteria or results in death it will be recorded as a SAE, otherwise it will be recorded as an AE.

Regarding the local anaesthetic, a large number of adverse events have been reported during clinical development, the majority related to the expected effects of the block and to the clinical situation rather than reactions to the drug, but are to be reported as follows:

- Nausea - AE
- Temporary paraesthesia - AE
- Headache - AE
- Urinary retention – AE, Unless it results in a UTI (Defined as >200 Leukocytes +/- bacteria in urine MCS and either symptoms of a UTI or sepsis with no other source identified). If this results in sepsis (As per SIRS Criteria) this will be recorded as an SAE, otherwise a simple UTI will be recorded as an AE
- Rare systemic toxicity from the local anaesthetic - The signs/symptoms the treating doctors and investigators will look out for are dysarthria, muscular rigidity, muscle twitching, unconsciousness, convulsions, hypoxia, hypotension, bradycardia, arrhythmias and cardiac arrest. If any of these are found with no other obvious cause, the local anaesthetic infusion is to be withheld. If the signs/symptoms resolve after the infusion is stopped, it is likely a causal relationship and any will be classified as a SAE and need to be immediately (Within 24hrs) reported to the principal investigator. Specialised local anaesthetic blood level tests may be ordered to help assess causality.

Other than the specific ones as stated above, this study defines any other complication a SAE when there is likely causal relationship between the procedure and/or local anaesthetic infusion and that complication such that it:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of an existing hospitalisation.
- Results in disability/incapacity

8.2 Time Period, Frequency, and Method of Detecting AEs and SAEs

All adverse events will be monitored for and recorded daily between recruitment and discharge from hospital (Usually 5+ days). Late adverse events will be assessed on follow up post laparotomy (Usually at approximately 4 weeks). This will be recorded on either the data collection tool or their electronic notes up to 2 months post procedure.

8.3 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigators to review all documentation (Including the electronic notes, laboratory, and diagnostic imaging reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in to the case report form (CRF).

For each adverse event, start and stop dates, action taken, outcome, intensity and relationship to study product will be documented. For non-expected adverse events, not outlined above, the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms will be documented

8.4 Evaluating AEs and SAEs

8.4.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event which is incapacitating and prevents normal everyday activities.

8.4.2 Assessment of Causality

The investigators will attempt to assess the relationship between the procedure/local anaesthetic infusion and the occurrence of each AE/SAE. The investigators will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy and other risk factors will be considered and investigated.

The causal relationship to the study product assessed by the Investigator will be assessed using the following classifications:

Not Related In the Investigator's opinion, there is not a causal relationship between the study product and the adverse event.

Unlikely The temporal association between the adverse event and study product is such that the study product is not likely to have any reasonable association with the adverse event.

Possible The adverse event could have been caused by the study Participant's clinical state or the study product.

Probable The adverse event follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study Participant's clinical state.

Definitely The adverse event follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

8.5 Follow-up of AEs and SAEs

All AEs and SAEs will be followed until resolution or until the Participant is lost to follow-up. Once resolved, the appropriate AE/SAE in the CRF will be updated. The investigator and treating doctors will ensure that follow-up will includes any supplemental investigation, such as local anaesthetic blood levels, to help establish severity and/or causality of the AE or SAE.

9 Participant Completion and Discontinuation

9.1 Participant Completion

Having the rectus sheath catheters placed in theatre and receiving the Ropivacaine boluses for 72hrs whilst being monitored on ward round.

9.2 Stopping Rules / Discontinuation Criteria

Infection of the catheter/wound; Any SAE; Patient request

9.3 Participant Withdrawal

The patient is able to withdraw at any point. If hey do they will be asked whether to withdraw from further data collection and whether they want their data already collected to be kept or discarded confidentially.

9.4 Early Termination of the Study

The study may be terminated prematurely by the principal investigator if:

- The number and/or severity of adverse events justify discontinuation of the study
- New data become available which raise concern about the safety of the study drug, so that continuation might cause unacceptable risks to participants.

After such a decision, all participating participants within two weeks will be notified as well as the Townsville Ethics Committee and chief medical officer of the MBH.

10 Data Analysis and Statistical Considerations

10.1 Hypotheses

Null hypothesis: Surgically placed pre-peritoneal catheters are superior to ultrasound placed rectus sheath catheters at reducing post-operative pain.

This hypothesis will be tested by the primary endpoint of total narcotic usage until day 3 post op and Patient blinded VAS scores at rest and coughing (0-10). These are both discussed below

10.2 Sample Size

Calculation of the sample size was performed with looking at the primary endpoint of total morphine usage post laparotomy. In a similar previous study the total dose of administered morphine was 62mg with a standard deviation of 16mg.[4] As stated above it was decided that a difference of 20% (12mg) would be considered clinically relevant, similar to this previous study.

A: Assuming α = 0·05 and β = 0·15 (a power of 85 per cent), a total of 62 patients (31 patients per group) would be required to needed to find there was no difference between each group.[10]

This means that with this sample size this study has an 85% chance of finding out if there is a statistically significant ($p<0.05$) 20% reduction in total narcotic usage until day 3 post op with surgically placed, instead of U/S guided rectus sheath catheters.

10.3 Statistical Analysis

All analysis will be performed by a qualified statistician at TTH. The first analysis will be to investigate if there are any significant difference between the demographics and primary clinical characteristics of each arm using Student's *t*-test or Fisher's exact test as appropriate.

Repeated measurements (pain scores) will be analysed by repeated measures ANOVA or ANOVA on ranks, with further paired comparisons at each time interval performed using the *t*-test or Mann–Whitney *U*-test as appropriate. Categorical data will be analysed using χ^2 analysis or Fisher's exact test where applicable. Normally distributed data such as morphine usage will be presented as means ± sd of the mean, non-normally distributed data are presented as medians ± quartiles (interquartile range), and categorical data are presented as raw data and as frequencies. Other testing may be done at the statistician's discretion.

The α level for all analyses was set as $P < 0.05$. The endpoints will then be analysed for any statistically significant differences. The arms will not be broken down further by demographics or primary clinical characteristics due to the small size likely causing spurious results.

If there is a false reading (eg morphine usage of 600mg instead of what was likely 60mg); the data and collection tools will be audited again. If the discrepancy cannot be found the patient result may be left out of the analysis, but will be clearly outlined that they were excluded and why in the report. Similarly, if there is missing information, the patient's result may be left out of the analysis, but will be clearly outlined why they were excluded in the report.

11 Data Management

The data collection sheets as well as the patient's electronic notes will be used to collect the data at first. Once a full data set for the patient is complete (Minimum of 2 months post procedure to record any late complications in the follow up), the data will then be completely de-identified and placed on a password protected excel spreadsheet. This will be audited by an independent surgical registrar. Once this is audited, the data collection tool and any re-identifiable materials will be disposed in confidential waste bins. This password protected completely de-identified spreadsheet will be kept on a private QH drive and the investigators personal drive to ensure 2 copies. This data will be kept for the minimum 15 years required.

12 Monitoring and Quality Assurance

Monitoring will occur via the three surgical doctors co-authoring this study in Mackay. They will be observing that the study is going as per protocol with recruitment, allocation and data collection. They will have routine meetings with the surgical and anaesthetic staff involved to ensure proper recruitment and protocol adherence.

12.1 Curriculum Vitae and Other Documentation

Please see attached

13 Investigator Responsibility

Except where the Principal Investigator's signature is specifically required, it is understood that the term 'Investigator' as used in this Protocol and on the CRFs refers to the Principal Investigator or an appropriately qualified member of the staff that the Principal Investigator designates to perform specified duties of the Protocol. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

Each Investigator will comply with the local regulations regarding clinical trials and the Investigator responsibilities outlined in the ICH GCP guidelines[1]

14 Study Report

The data in the de-identified spreadsheet will be analysed by the Principal Investigator and sent to an independent statistician at the TTH or James Cook University for rigorous statistical analysis. The final report is to be written by all investigators and is to be published in a major surgical or anaesthetic journal as well as likely changing local policies at the MBH.

15 Administrative Procedures

15.1 Ethical Review Committee

The Principal Investigator will be responsible for reporting any serious adverse events to the Reviewing Ethics Committee and site governance Office as soon as possible, and in accordance with the guidelines of the State Guidelines.

15.2 Regulatory Authorities

As the equipment and medications used are all within TGA approved indications, no special regulatory approval has been sought.

In agreeing to the provisions of the Protocol, these responsibilities are accepted by the Investigator.

15.3 Informed Consent

Before recruitment and enrolment into the study, each prospective candidate will be given a full explanation of the nature and purposes of the study, as well as a copy of the Participant Information Sheet to review. Once the essential study information has been provided, and the doctor is assured that the patient understands the implications of participating in the study, the participants will be asked to give consent to participate in the study by signing the informed consent form. The consent forms shall be signed and dated by the appropriate parties. A notation that written informed consent has been obtained will be made on the participant's CRF. The completed consent forms will be retained by the Investigator and a copy of these will be provided by the Investigator to the participant.

If the patient is unable to consent, the next of kin will be given the same information and the same opportunity to consent for them. This process will be the same as per their procedure consent.

15.4 Emergency Contact with Investigators

All participants and doctors running the protocol will be able to contact any investigator if there any issues.

15.5 Notification of Primary Care Physician

Notification of enrolment into the study will be done via the discharge summary.

15.6 Protocol Amendments

Once the final Protocol has been issued and signed by the Investigator and the authorised signatories, it shall not be informally altered. No changes (amendments) to the Protocol may be implemented without prior approval the Townsville Ethics Committee and site governance officers other than administrative changes (Eg spelling).

15.7 Protocol Compliance

The three surgical investigators including the head of surgery in Mackay will be ensuring protocol compliance. Should there be questions or consideration of deviation from the protocol, clarification will be sought from one of these investigators or the Principal Investigator.

Only when an emergency occurs that requires a departure from the Protocol for an individual will there be such a departure. The nature and reasons for the Protocol violation/deviation are to be documented and the principal investigator informed.

15.8 Archives: Retention of Study Records

All de-identified source documents will be kept for the minimum of 15 years.

16 References

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