**A Phase 1 feasibility study: The validation of Gastrografin measurement in postsurgical samples following low anterior resection where the rectal tube is flushed with Gastrografin:**

**Project Protocol**

**Main Study Site**

|  |  |
| --- | --- |
| **Study Site** | **Principal Investigator** |
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**List of abbreviations**

|  |  |
| --- | --- |
| AL | anastomotic leak |
| ARTG | Australia register of therapeutic goods |
| ASA | American society of Anaesthesiologists |
| CRP | C-reactive protein |
| CT | computer tomography |
| DECT | dual emission CT |
| DFG | drain fluid Gastrografin |
| DFL | drain fluid lipase |
| ELFTs | liver function tests |
| EOI | expression of interest |
| FBC | full blood count |
| HREC | human research ethics committee |
| HU | Hounsfield units |
| Lap | laparoscopic |
| MRN | medical reference number |
| NG | nasal gastro tube |
| Post op | post operative |
| Pre op | pre operative |
| QID | four times per day |
| RACS | Royal college of surgeons |
| RBWH | Royal Brisbane & Women's Hospital |
| RCT | randomised clinical trial |
| TGA | therapeutic goods administration |

**Project Summary**

Anastomotic leakage (AL) is a serious complication of intestinal surgery, resulting in increased morbidity and mortality. Current approaches to early detection of AL are nonspecific and insensitive. As a consequence, AL are often diagnosed at a later stage with the presentation of clinical symptoms and often secondary complications. In our subsequent studies we propose utilising a commonly used radiological solution, Gastrografin, as a biomarker of early detection of AL.

Gastrografin is a water soluble, contrast solution commonly used for abdominal CT (computer tomography). In clinical practice, when administered orally or as an enema Gastrografin acts as a radiological contrast for the detection anastomotic leaks. It is also employed in regular clinical practice in small bowel obstruction and ileus.

Our feasibility study aims to assess safety and optimise the technique and conditions required to reliably detect Gastrografin in surgical samples by Dual Emission CT (DECT)

The outcomes of this Phase 1 feasibility study and the separate validation study are important in the development of the standard operating protocols for our proposed main study *“Drain fluid Gastrografin as a sensitive biomarker for early detection of anastomotic leaks after low anterior resection”.*

**Introduction**

Gastrografin (Diatrizoate, also known as amidotrizoate meglumine and sodium amidotrizoate) is a hyperosmolar water-soluble iodinated radiological contrast media. It is recorded as ARTG ID: 10684 on the Australian Register of Therapeutic Goods maintained by the TGA.[[1]](#endnote-1)

**Gastrografin safety and applications**

Gastrografin may be administered per orally or as an enema. It is used routinely in clinical practice. Its safety has been established in a number of randomised trials.[[2]](#endnote-2) A meta-analysis of contrast enemas found that procedures involving Gastrografin were safe with only 1 reported complication of the 1169 procedures studied. Gastrografin and Urografin were the most common agents used in these radiological procedures.[[3]](#endnote-3) This study for AL was found to have a negative predictive value of 98.4% and a positive predictive value of 64.6%.

Aside from its routine use in radiology, Gastrografin has been safely employed in patients with small bowel obstruction and assessed as a prokinetic in prolonged post-operative ileus.[[4]](#endnote-4),[[5]](#endnote-5)

**Gastrografin Measurement**

Dual emission CT scanning (DECT) is a new technology that allows acquisition of 2 datasets from the same anatomical region at different voltages. [[6]](#endnote-6) In contrast to single-spectrum imaging, which depicts the organs based on spatial distribution of the object attenuation, DECT is sensitive to the chemical composition. Hence, DECT is capable of differentiating materials with different atomic numbers and the iodine in Gastrografin is able to be simply measured using a protocol described in the literature.

**Pelvic Drains**

Drains are commonly employed after pelvic surgery, primarily to drain accumulated blood but also any infected collections. A meta-analysis has looked specifically at pelvic drain use and found no difference in outcomes between those with and without drains.[[7]](#endnote-7) It is recognized that many surgeons prefer to drain the pelvis by placing pelvic drains post surgery Participating surgeons in this study routinely place a pelvic drain after a low anterior resection with an extra-peritoneal anastomosis.

**Rectal Tubes**

In our surgical unit it is routine practice to place a 28G Foley catheter per-anally and across the sphincter in all patients undergoing a rectal resection with an extra-peritoneal anastomosis. There is evidence that transanal tubes are effective and safe in decreasing the rate of clinically significant anastomotic leaks and mitigating the clinical consequences of leakage. [[8]](#endnote-8) Rectal tubes are routinely flushed with saline QID following surgery to prevent blockage.

**What this project adds to the body of literature**

The described technique of measuring Gastrografin by DECT is novel and not been previously reported. This project aims to establish the safety and feasibility of employing Gastrografin flushes of the rectal tubes and how it compares to the the standard of care of Saline flushes.

Our hypothesis is that the subsequent detection of Gastrografin in drain fluid following flushing of rectal tubes with Gastrografin, will allow the early diagnosis of anastomotic leakage. This hypothesis will be tested in a subsequent proposed study. Our findings will establish the approach, techniques and standardised DECT protocol for the measurement of Gastrografin in surgical drain fluid.

**Preliminary studies**

Our preliminary in vitro studies have contributed to the development of DECT protocol (Appendix 1) to detect the presence of Gastrografin in a sample solution of sterile water or drain fluid. The lower limit of detection of a solution containing Gastrografin was at a concentration of 0.097% which correlated to an iodine density of > 1 mg/ml. We have established measurements of iodine density above 1mg/ml to represent a positive result for the presence of Gastrografin in a solution. HU will be used as a secondary marker.

Measurements for iodine density and HU in sterile water and drain fluid were comparable when the sample was scanned at day 1 and rescanned at 8 weeks, confirming the stability of Gastrografin in drain fluid and sterile water over 8 weeks. Using the DECT scan parameters above we found inter-scan and intra-scan measurements of Gastrografin were reliable and reproducible.

**Project Aims**

* Develop and validate a standardised protocol for the measurement of Gastrografin in surgical fluid and stool.
* Assess tolerance and safety of rectal tube flushes with Gastrografin
* Proof-of-concept (POC) assessing Gastrografin as biomarker of AL
* Assess feasibility of a subsequent multicentre study investigating Gastrografin as a sensitive biomarker of AL

**Project Design**

This is a single-site, open label observational study assessing the safety of using Gastrografin for flushing of rectal tubes post surgery. This study will lead to establishing the optimal parameters for the detection of Gastrografin in surgical fluid and stool and assessing the feasibility of a larger multicentre study investigating Gastrografin as a sensitive biomarker of AL. This feasibility study is prospective and requires patient consent for participation.

We propose a sample number of 10 patients in this single arm study.

The proposed study will be performed in accordance with Good Clinical Practice (GCP) guidelines. The safety of participants will be monitored closely by the principal investigator and clinical team during hospital admission.

**Participants**

The project will recruit patients undergoing a rectal resection with an extra-peritoneal anastomosis (within 10cm of the anal verge) and without a covering loop ileostomy. Only patients who have a rectal tube and a pelvic drain tube inserted at surgery will be invited to participate in the study. The drain fluid is normally discarded at nursing shift changes as part of post surgical care.

The collection of the drain fluid post-surgery is non-invasive, presents no additional risk and of no inconvenience to the participant.

Participation in the study is voluntary and will not influence patient care.

**Inclusion Criteria**

Patients undergoing rectal resection and extra-peritoneal anastomosis without a covering loop ileostomy

Placement of a rectal tube in the neo-rectum

Placement of a pelvic drain at surgery

Satisfactory anastomosis at surgery

Indication for surgery may include benign or malignant disease

**Exclusion Criteria**

Age less than 18 years

Inability to give written consent

Proctocolectomy and ileal pouch surgery

Absence of drain placement at surgery

**Expected Duration of Project**

It is expected that this study will commence in 01 November 2018 and be completed in 01 May 2019.

**Methodology**

Patients meeting the inclusion criteria will be invited to participate in the study and will be allocated in the following Group (Table 1).

**Table 1: Allocation of participants into study group**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **Inclusion criteria** | **Study Group** | **Sampling for DECT** |  |
| N=10 | Rectal resection and extra-peritoneal anastomosis (no covering loop ileostomy) | Rectal tubes flushed with 30 mL Gastrografin QID | 10 ml of rectal tube fluid (Day 1) and  10 ml of drain fluid (daily) |

N= number of patients aimed for recruitment

The first 10 eligible patients fitting the selection criteria will be invited to participate in the study.

**Gastrografin Flushes**

Rectal tubes are routinely flushed with 30 ml of saline QID, daily as part of post-surgical care, with no discomfort to the patient. The output of the flushes is discarded daily.

Rectal tubes flushed with Gastrografin: Patients will receive rectal flushes with 30 ml of Gastrografin QID, daily. The Gastrografin flushes will replace the standard saline flushes.

The flushing of rectal tubes with Gastrografin will be documented, detailing participant ID, name, DOB, date, volume of Gastografin, time.

Measurement of Rectal tube Gastrografin

To establish the individual baseline intra-luminal Gastrografin level, a 10 ml sample will be collected at Day 1 post-surgery and quantitated with DECT scanning. The methodology for the quantitation of Gastrografin in biological fluids has been established in a basic science paper looking at serial dilutions and stability of Gastrografin *in vitro*.[[9]](#endnote-9)

Measurement of Drain fluid Gastrografin levels (Day 1 to 5 or longer if drain remains in situ after 5 days)

Drain fluid samples will be collected from Bellovac drains 30 mins after administration of the morning rectal tube flush at 0730am. The drainage bag (A) is removed and the bellows emptied to a sterile plastic pot. A 10 mL sample will be collected at Day 1, 2, 3, 4, 5 for the measurement of Gastrografin by DECCT or until drain removed as clinically indicated.

A

The collection of drain fluid samples presents no risk, discomfort or inconvenience to the patient.

**Safety Evaluation**  
Safety of participants will be monitored daily during the admission and followed up with a telephone call 7 days post discharge. Any adverse events will be reported and documented ( as below). The first day of adverse event, will coincide with the administration of the first recatl tubel flushing with Gastrogarfin. All adverse events will be reported to the principal investigator.

Reporting Adverse Events (AE):

Onset of AE (Date and time)

Resolution of AE (Date and time)

Severity (Mild, Moderate, Severe, Life-threating)

Action Taken

Outcome of the event

Relationship to Gastrogarfin Flushing of rectal tubes (Probable, possible, unlikely)

Signature of PI

**Data Collection**

Eligible patients will be informed of the study and invited to participate by the study coordinator at the pre-admission clinics. Only patients who have provided written consent will be enrolled in the project. Patient demographics, surgery details and post-surgical information will be obtained (Data Fields for collection listed in Table 2). All patient information will be de-identified by the assignment of a unique numeric code, known only to the investigators listed on this project.

De-identified data will be entered into Redcap data capture system, which is encrypted, and password protected. Passwords will be issued only to investigators assigned to this study. Patient consent forms will be stored in key-locked cabinets for 7 years after publication of the findings. Any datasheets generated during this study will be destroyed once the data has been entered. Electronic files will be erased 7 years after publication of findings.

All statistical analysis will use de-identified data and only the principle investigator will have the key to re-identification.

A research co-ordinator employed by the principle investigator will be responsible for the collation and input of data.

The outcomes of the study will be categorised into patient demographics and surgical details, clinical course and Gastrografin measurement.

**Table 1: Data Fields for collection**

|  |  |
| --- | --- |
| **Demographics** | **Clinical course:** |
| Study ID | Anastomotic leak (yes/no)  Grade A/B/C |
| MRN | Return to Operating theatre (yes/no) |
| Name | Date Return to Operating theatre |
| Date of Birth | Operation type |
| Gender | Surgical Complications  Medical complications  Graded by Clavien Dindo classification [[10]](#endnote-10) |
| Weight | Date of admission |
| Height | Date of discharge |
| Diagnosis | Length of stay |
| Date of Diagnosis | Post op imaging  Drain in pelvis (Y/N) |
| Co-morbidities | Day full diet established |
| ASA | NG tube insertion |
|  | Nausea/ Vomiting |
| Operation | Histology |  | | |
| Operation date |  |  | |
| Operation duration |  |  | |
| Peri-operative antibiotics |  | |  | | |
| Surgical approach (Lap/Open) |  | |  | | |
| Tumour distance from anal verge (in cms) |  | |  | | |
|  |  | |  | | |
|  |  | |  | | |

**Schedule of Assessment**

Participants in the study will undergo routine blood testing as part of inpatient post surgical care and daily drain fluid collection and analysis by DECT as protocoled in this study. The daily assessment schedule is summarised in Table 2.

**Table 3: Schedule of Assessment**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Discharge  Day |
| Demographics | X |  |  |  |  |  |  |
| Clinical Course |  |  |  |  |  |  | X |
| Adverse events |  | X | X | X | X | X | X |
| Rectal Tube Gastrografin |  | X |  |  |  |  |  |
| Drain Fluid Gastrografin |  | X | X | X | X | X |  |

**Post discharge**

|  |  |  |
| --- | --- | --- |
|  | Phone interview (7 days post op) | Follow up consulation |
| Adverse Events | X | X |

**Drain position**

Drains are placed in the pelvis at surgery. A 19 Blakes drain is used and placed on suction as soon as practical to prevent formation of clotted blood that may impair the drainage of pelvic fluid. It is possible that drains may be malpositioned or dislodged and this may lead to a false negative result in the setting of AL. Whilst it is not intended that patients should undergo routine imaging to confirm position, the majority of those experiencing a clinical AL will have a CT performed and position of the drain can be assessed.

**Blinding of samples for CT**

The drain fluid samples will be blinded to the reporting radiologist. Results of the CT studies of DFG will be made available to the treating clinicians and management of the post-operative course will be at the clinician’s discretion.

**Patients Safety**

This feasibility study invites patients consecutively into Group 1; patients receiving rectal tube flushes with Gastrografin. Gastrografin’s safety in contrast enemas has already been established in clinical care and is a component of usual investigation of patients with and without an AL. There is no risk to the patients in sampling pelvic drain fluid as this is normally discarded at nursing shift changes. There is no patient exposure to ionising radiation as a consequence of the study.

There are no additional phlebotomies required for the study.

The study aims to assess the feasibility and accuracy of Gastrografin measurement in drain fluid.

**Colorectal Surgeon Survey**

A survey distributed through the Colorectal Surgical Society of Australia and New Zealand assessed the clinical practice of the 88 respondents. 98% of respondents use Gastrografin enemas in routine clinical practice.



**Adverse Events**

Daily assessment for the occurrence of adverse events will be assessed and recorded. Following discharge, a phone call from Dr Clark’s practice nurse will further asses for adverse events and recovery7 days following discharge. A final assessment will be undertaken at a follow up consultation with PI Clark at six weeks post operation.

**Funding**

An EOI grant application has been submitted the RBWH Foundation and an additional grant application has been submitted to the RACS Foundation Small Project Grant scheme. Existing funds are available and held in a tied fund at the Royal Brisbane and Women’s Foundation.

**Dissemination of results**

The final manuscript will be submitted to peer reviewed journals for the purpose of publication. No identifiable data will be included.

**Ethical Consideration**

This project will be submitted to the St. Vincent’s Health and Aged Care (SVHAC) Human Research Ethics Committee (HREC) for review. HREC applications will also be submitted for participation by collaborative sites.

**Benefit to the Community**

The morbidity suffered along with the long term consequences of anastomotic leak mandate efforts to identify this serious complication at an early stage. Early diagnosis has proven to be elusive and if measurement of Gastrografin levels in drain fluid ultimately achieves this aim, there will be a significant benefit to the individual patient and a considerable cost saving to the health system.

**Appendix I: Standard operating protocol:**

**Measurement of Gastrografin in surgical drain fluid by Dual Energy CT (DECT)**

**Background**

The benefit of DECT is achieved via its ability to distinguish between materials based on their spectral properties; a material’s capacity to attenuate x-ray photons at different photon energies. Materials interact with x-ray photons in several ways including the Compton effect and the photoelectric effect[[11]](#endnote-11). DECT operates on the principle that two different x-ray spectra will cause a material to absorb x-ray photons differently according to these interactions. This particularly applies for the photoelectric effect which is dependent upon a materials properties, such as the atomic number, electron density and K-edge electron energy. The widely used CT contrast agent iodine has a high atomic number (Z = 53) which results in a strong photoelectric effect. This photoelectric effect and spectral behaviour can be measured by DECT and can be used to detect and quantify iodine containing substances, such as Gastrografin[[12]](#endnote-12).

**DECT Scan Protocol and Sample Measurement**

Daily 10ml samples of drain fluid will be collected into 50 ml sterile jars and stored at room temperature. All samples will be scanned via the same dual source CT system (Somatom Force, Siemens Medical Solutions, Forchheim, Germany) in the same radiology department by the same senior CT radiographer. The samples will be placed flat onto the CT table and evenly spaced by 10 cm. The samples will be scanned within 4 weeks of sample collection.

The dual energy protocol with acquisition parameters of 80 kV and Qref mAs of 100mAs on the A tube and sn150 kV and QRef mAs of 67mAs on the B tube will be used to scan each sample. To deliver a constant radiation dose for all scans, no dose modulation will be utilised. Each detector will be collimated to 128×0.6mm with a flying focal spot, and a pitch of 0.7 will be applied. Images will be reconstructed with a dedicated Br40 reconstruction algorithm. Slice thickness and increment will be 1.0mm and 0.7mm, respectively. Two individual stacks of images for each detector (80 kV and sn150 kV images) and a DE mixed images will be reconstructed. The latter will contain weighted information from both detectors with a weighting factor of 0.6 (60% from the 80 kV scan and 40% from the sn150 kV scan) thus approximating regular 120 kV images.

After reconstruction, images will be transferred to the same workstation with dedicated commercial post-processing software (Syngo Dual Energy, Siemens Medical Solutions, Forchheim, Germany). The dual energy datasets will be analysed using the LiverVNC software where iodine density and HU will be measured for each sample without any manual adjustments to the algorithm.

Two separate region of interest (ROI) measurements will be use to measure the HU and iodine density units of each sample. The ROI measurements will be obtained via coronal reformats to the right and left of the solution midline, each ROI measuring 10mm^2. All measurements will be performed by the same radiologist who will remain blinded to the samples.

Samples will be re-scanned twice during the course of the study, and if significant discrepancies between results are present, the solutions will be rescanned twice more. The two individual HU and iodine concentration results for each sample will be recorded as per the data collection described in the protocol.

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