**LIGIT TRIAL**

**Impact of post-operative Lidocaine Infusion on GastroIntestinal Tract function in patients undergoing laparoscopic colorectal resections.**

A double-blind placebo controlled randomised trial of 24 hour post-operative intravenous lidocaine infusions effect of return of gastrointestinal function following elective colorectal resection in adult patients.

Version number: v1.1

Project Team Roles & Responsibilities

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Resources

Given the investigators are unlikely to attain a funding grant for this study this will be performed with no additional resources or funding.

Background

With improvements in minimally invasive surgery and enhanced recovery programmes the recovery process from uncomplicated colorectal resections is relatively swift, save from the impact of prolonged stasis of the gastrointestinal tract which can affect up to 30% of patients (Mao 2018). This delay in return of gastrointestinal (GI) function can manifest as nausea, vomiting, abdominal distension and absence of flatus or bowel motions. It is the most frequent reason for delayed recovery and discharge after laparoscopic colectomy.

The pathophysiology of delay to return of GI function is multi-factorial, influenced by direct manipulation of the GI tract during surgery, the release of inflammatory mediators and sympathetic stimulation as a response to surgery. These effects are often exacerbated by the use of opiate analgesia in the post-operative period. The use of intravenous lidocaine is thought to overcome some of these factors.

Intravenous Lidocaine has its effect by inhibition of spontaneous impulse generation from injured peripheral nerves and dorsal root ganglions (Devor 1992). Postoperative pain is often the result of an inflammatory process which has been shown to be ameliorated by IV lidocaine (Koppert 2004). Lidocaine has anti-inflammatory effects mediated through the inhibition of G-protein coupled receptors and polymorphonuclear cells (Hollman 2000). The culmination of the above pathways and the growing evidence that post-operative lidocaine limits opiate use lends to the hypothesis that post-operative lidocaine infusion may bring about an earlier return of GI function following colorectal resections.

Literature review

There is growing evidence that intravenous lidocaine reduces post-operative pain scores and opioid requirements and some evidence it shortens return of gastrointestinal function. A meta-analysis published in 2019 in *Techniques of Coloproctology* reviewed IV lidocaine and its effect of GI function. It included 9 RCT ranging in size from 18-60 patients. None of these RCTs had GI function as the primary endpoint. How-ever this meta-analysis found nearly a 10-hour reduction in time to first bowel motion, a 7-hour reduction in time to first flatus in the open sub-group. It also found significant reduction in post-operative ileus with an OR 0.32 95% CI (0.15-0.71). There was no significant difference in time to resumption of diet, but this may be affected by enhanced recovery programmes.

A Cochrane review of the subject has found insufficient evidence to determine a statistically significant difference however it did find a relative risk of 0.36 for post-operative ileus (0.15-0.87) and an average of ~ 8 hours reduction in time to first bowel motion (3.1-12.7) however there is significant heterogenicity amongst the studies included and the reviewers felt these findings crossed the line of clinical non-relevance.

Rationale

There have been a number of RCT comparing lidocaine with placebo and assessing the effect on pain in the post-operative period. A number of these have assessed bowel function as a secondary end-point however very few have assessed this as a primary end-point. With well-established evidence that IV lidocaine is at least equivocal to standard post-operative care with regards to pain scores the next main question to be answered is, can it reduce the duration until return of GI function. To date there have been no RCT with GI as its primary outcome. There is one large RCT currently recruiting in Edinburgh (ALLEGRO Trial) which aims to look at this outcome however they are only assessing IV lidocaine infusion for 6-12 hours post-operatively. This study will aim to asses effect of IV lidocaine infusion in a southern hemisphere population and with an extended duration of IV lidocaine infusion.

Research questions/aims/objectives/hypothesis

The trial will aim to assess if, in adult patients undergoing elective laparoscopic colorectal resection, the addition of post-operative lidocaine infusion in comparison to placebo results in an earlier return of gastrointestinal function as determined by the time to first flatus or the passage of bowel motion and the tolerance of solid diet.

The hypothesis is that the exposure group will have an earlier return of GI function with an earlier discharge date.

**Proposed trial design**

We propose to perform a randomised control trial comparing IV lidocaine 24hr post-operative infusion with IV saline placebo for all patients who have undergone an acute or elective laparoscopic colonic resection at Austin Hospital.

Primary end-point:

* Duration to ‘Return of gastrointestinal function’ using the validated GI-3 requirement:
	+ Time to tolerating solid diet and passage of flatus OR bowel motion”.

Secondary end points:

* Incidence of post-operative ileus (POI)
	+ Defined as the presence of ≥2 of the following criteria on or after postoperative day 4:
		- * moderate to severe nausea or vomiting
			* inability to tolerate a solid or semisolid diet
			* moderate to severe abdominal distension
			* absence of flatus and stool
			* and radiological evidence of ileus on x-ray (H.Mao)
* Time to discharge
* Pain scores as measured by validated visual analogue scale
* Oral opiate requirement equivalent (inclusive of IV or oral administration)
* Complications
	+ Lidocaine related adverse outcomes
		- Minor – peri-oral tingling, tinitis, ECG changes related to IV lidocaine
		- Severe – Seizures, ECG changes, arrhythmia

\*Assessed by educated nursing staff as per lidocaine infusion protocol/clinical notes

* + All other complications as per Clavian-Dindo classification.

Power calculation

With respect to our composite primary endpoint of return of gastrointestinal function (GI-3), sample size analysis using the z test for two independent means revealed a required number of patients of 25 per group to detect a 10 hour difference, with a two-tailed a = 0.05 and power of 80 %.

We used the results of a recently published meta-analysis (reference here) that had a mean time to first bowel movement of 61.6 hours and SD of 12.4 hours in the control group and a difference of 7.9 hours between groups for our estimation.

The same meta-analysis also demonstrated that time to first flatus was achieved before first bowel motion, therefore the greater of these two measures (time to first bowel motion) was used to meet the sample size requirement for our composite primary outcome. The total number of patients per group was increased to 28 to compensate for possible dropouts.

Ethics

 Ethical review submitted via ERM to Austin Health Human Resources Committee.

Study protocol

 Randomisation + allocation

Pharmacy will provide assistance with randomisation and formulation of blinded study drug for administration. Two study drugs will be formulated – one being placebo (normal saline) and the second being the active formulation of lidocaine (20mg/ml – 1000mg of lidocaine diluted in 50ml of normal saline)

 Blinding

Patients, all ward-based health providers and data collectors/analysers will be blinded.

If option one is used the anaesthetist and anaesthetic technician will be unblinded and be responsible for the infusion setup. We realise they will likely be involved with analgesia administration in recovery and will factor this into the data collection and account for this in analysis as this is a potential for bias. They will have nothing further to do with the study protocol/data collection or analysis.

 Recruitment

All eligible patients will be introduced and offered inclusion into the study at the pre-operative clinic discussion or pre-operatively on the day of admission. Clinicians involved in the patient care will be available to explain study details and rationale. The patient and relatives will be given written information on the study protocol, aims of investigation and requirements of the patient involved. A full informed consent process will be completed either in clinic or at the time of admission for surgery.

 Inclusion criteria:

All patients >18 years undergoing elective laparoscopic/hybrid colorectal resections for benign or malignant conditions at Austin hospital during the study period. Except those with exclusion criteria.

 Exclusion criteria:

 Contraindications to IV lidocaine:

* Known history of allergy or hypersensitivity to Lidocaine (lignocaine) or other amide-type local anaesthetic.
* Stokes-Adams syndrome or any type of heart block or other high-risk arrhythmias.
* Severe shock
* Myasthenia gravis
* Serious diseases of the CNS or of the spinal cord

 Other exclusion criteria:

* Childs Pugh A or worse liver disease
* CKD with eGFR <40ml/hr
* Chronic use of opioid analgesia or local anesthetics
* Patients will be excluded if they were unable to participate in postoperative assessments because of language difficulty, postoperative confusion, or cognitive impairment.

 Drug administration

Intraoperative lidocaine infusions are now standard practice for colorectal resections at Austin hospital and therefore this will be administered to both exposure and placebo group during the study period. This will be run at a standard rate of 1.5mg/kg intraoperatively.

At the completion of the case the patient will then be allocated to lidocaine or placebo. The lidocaine infusion will cease and the patient will be changed to the blinded study drug to run at 1mg/kg/hr infusion for 24 hours on the ward – as per Austin protocol.

The remainder of the anaesthetic will be as per a standardised plan (as per the recent ROCKET trial regime) aside from where it is required to be adjusted at the clinician discretion.

Data collection:

 Primary outcome

* Patients will be reviewed 2-4 hourly for:
	+ Symptoms of local anaesthesia toxicity – as per Austin protocol
	+ Pain scores using a visual scale
	+ Nausea/vomiting – presence or absence
	+ Passage of flatus
	+ Passage of bowel motions.
* Pts will be asked to record as a one-off measure
	+ Time of first flatus
	+ Time to first bowel motion

 Secondary outcomes

* Opioid requirement will be determined from PCA usage and electronic med-charts.
* Date of discharge from electronic discharge documents
* Pain scores from visual analogue pain scores at 2-hour intervals
* Complications will be recorded during admission and for 30 days following discharge.

Baseline Data-points for comparisons between two groups:

 Demographic data:

* Age
* Gender
* Ethnicity
* ASA
* BMI
* Charlston Co-morbidity Index
* Pre-existing opiate therapy
* Smoking status

 Operative Data

* Operation
	+ Neoadjuvant therapy
	+ Stoma
* Surgeon skill level
* Operative duration
* Histology
	+ Benign/Malignant
* Induction agent
* Intra-operative opiate use
* LA infiltration
	+ Location
	+ Volume

 Statistical analysis

Participant withdrawal

Participants may be withdrawn from the study in case of a protocol violation or if the intended surgery did not proceed due to unforeseen reasons. Patients may also withdraw at any time of their own volition. The reasons for withdrawal will be recorded and depending upon the patient’s wishes any information gathered up to that time can either be discarded or used as an ‘intention to treat’ analysis.

If there are a significant number of withdrawals such that it may affect power size the study will be reviewed and the reason for withdrawals assessed to determine if the study should be suspended or further recruitment performed.

Research Activities:

* + Participant commitment
		- Participants commitment will only involve research diary that is to be completed during their post-operative stay. There will be no further commitments by participants in the pre-admission period or following discharge.
	+ Project duration
		- The project will continue until recruitment is completed. This is expected to take 6-8 months from beginning recruitment. The maximum project period would be 24 months.
	+ Participant follow-up
		- Follow up will continue to for 30 days from day of discharge to identify any post-operative complications. This will involve a phone call at 30 days from discharge to the participants to ensure they have not required admission to another hospital or treatment by their GP.

Data Management:

* A spreadsheet-based database will be established by the investigators. Direct data entry into the spreadsheet immediately after collection aims to improve efficiency, reduce entry errors, minimize data queries and maximize data completeness.
* Data will be recorded in a dedicated standardized data extraction form and transcribed to electronic disk where it will be logged in the spreadsheet format for later recall and analyses. Data will only be identified by code number for each patient, and the links to patients’ records, along with data records themselves, will be stored in locked cabinets in the Colorectal Fellow Office at Austin Health. There will be no identification of patient details and all patients will be assigned anonymous identifiers and actual entities will remain confidential and secure under the supervision of the principal investigators. This includes patient name, date of birth, hospital number, home address or telephone contact number, or any other personal information recorded in any publication arising from this project.

Results, Outcomes and Future Plans

* Plans for return of results of research to participants
	+ During the consent process patients will be given the option of having the manuscript posted to them to see the results of the study. They will also be given the option of determining if they were in the control of placebo arm at the completion of the study period.
* Plans for dissemination and publication of project outcomes
	+ Project will be published as a randomised control trial in a peer-reviewed journal with complete anonymity to participants involved.
* Project closure processes
	+ The project will close when the final patient has been recruited, completed surgery and the 30 day post-operative period.
* Plans for sharing and/or future use of data and/or follow-up research
	+ No plans for future use of data.