LIG Trial - Lignocaine in gastroscopy

Investigators

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Aim

The aim of this randomised controlled trial is to determine whether the use of a therapeutic dose of lignocaine enhances elective outpatient gastroscopy episodes.

Background

Gastroscopy is a common outpatient elective procedure involving insertion of a flexible tube with a camera (an endoscope) through the mouth into the oesophagus, stomach or duodenum.[1] In 2016-2017, data from the National Hospital Morbidity Database found that 505,544 hospitalisation for gastroscopy occurred in public and private sectors throughout Australia.[2] A gastroscopy is indicated to investigate symptoms of upper gastrointestinal disease, including cancer, to treat upper gastrointestinal conditions, monitor chronic conditions and to perform biopsies to assist with diagnosis, assess treatment surveillance or efficacy.[3]

Lignocaine is a local anaesthetic agent commonly used for multiple purposes in anaesthetic practice and may assist with improved endoscope insertion conditions, less post gastroscopy discomfort and faster time for discharge to recovery. Favourable characteristics of lignocaine include its anti-nociceptive actions, with an established role as an effective analgesic agent for visceral pain and a reduction in propofol requirements during surgery which may assist in a faster recovery from procedural sedation.[4,5]

A similar trial of this nature for gastroscopy has not been conducted, however, Foster et al in a randomised controlled trial demonstrated that lignocaine administration of a therapeutic dose of lignocaine followed by an infusion of 4mg/kg/hr post titration of sedative agent, decreased propofol requirement by 50%, decreased immediate post-colonoscopy pain and fatigue.[6] No difference was found regarding episodes of desaturation, endoscopist comfort and times for discharge to recovery.[6] Similarly, in patients requiring a

more extensive procedure than a standard gastroscopy, Kim et al. showed that patients receiving endoscopic submucosal dissection for gastric neoplasm, the lignocaine group had a lower requirement for opioid medications, reached sedation faster, had less patient movement during the procedure, and statistically significant decreases in post-procedural throat pain and epigastric pain at 6 hours.[7]

References:

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3) Cohen J, Greenwald D. Overview of upper gastrointestinal endoscopy (esophagogastroduodenoscopy) [Internet] 2019. UpToDate. Wolters Kleuwer. Netherlands. [updated 2018 May] [Cited 2019 Oct 07].
4) Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine. Anesthesiology. 2017;126(4):729-37.
5) Hans GA, Lauwick SM, Kaba A, Bonhomme V, Struys MM, Hans PC, et al. Intravenous lidocaine infusion reduces bispectral index-guided requirements of propofol only during surgical stimulation. Br J Anaesth. 2010;105(4):471-9.
6) Forster C. et al. Intravenous infusion of lidocaine significantly reduces propofol dose for colonoscopy: a randomised placebo-controlled study. Br J Anaesth. 2018 Nov;121(5):1059-1064. doi: 10.1016/j.bja.2018.06.019. Epub 2018 Aug 1
7) Kim JE, Choi JB, Koo BN, Jeong HW, Lee BH, Kim SY. Efficacy of Intravenous Lidocaine During Endoscopic Submucosal Dissection for GastricNeoplasm: A Randomized, Double-Blind, Controlled Study.Medicine (Baltimore). 2016 May;95(18):e3593. doi: 10.1097/MD.0000000000003593.

Methods

This single centre, double blind, randomised trial will enrol 100 patients undergoing elective gastroscopy.

This trial has been registered on the Australian and New Zealand Clinical Trials Registry before commencement of enrolment. A Clinical Trial Notification to the Therapeutic Goods Administration has been made for the use and indication of normal saline (NaCl 0.9%) and lignocaine in this clinical context.

Inclusion criteria

1. Adults (≥18 years) undergoing elective gastroscopy with low aspiration risk.

Exclusion criteria

1. Patient refusal
2. After-hours or emergency gastroscopies including indications for upper gastrointestinal bleed.
3. Contraindication or allergy to lignocaine.
4. <18 years old or >80 years old
5. Pregnant patients
6. Patients at high risk for aspiration or requiring intubation
7. Gastroscopy solely performed by topicalisation of the throat
8. Patients requiring or opioids during gastroscopy

Randomisation

Eligible patients will be provided with an explanation of the study and a participant information and consent form. Consenting patients will be randomly assigned from a computer-generated list (1:1), stratified to either lignocaine or placebo groups. Randomisation will be completed by trained and dedicated research staff in the online Research electronic data capture (REDCap Consortium, Vanderbilt University, Nashville, TN database).

Study drug administration

The pre-prepared study drug will be administered as a loading dose of 1.5mg/kg of lignocaine as a single dose to a maximum dose of 120mg of lignocaine (not exceeding >3mg/kg), prior to titration of propofol. If the gastroscopy is continuing beyond 20 minutes, a further dose of lignocaine will be administered up to a total maximum dose of 3mg/kg, no further lignocaine will be administered. This RCT is pragmatic, therefore, the total dose of propofol will be collected but the dose is at the discretion of the anaesthetist, titrated to endoscopist requirements.

For patients in the placebo group, a similarly labelled syringe of saline 0.9% will be administered, followed by propofol to facilitate the procedure.

The patient, anaesthesiologist, endocscopist, nurses, outcome assessors and data analysers are blinded to the intervention.

Perioperative Management

All patients will receive preoperative care as per usual practice. We will record preoperative fasting times and use of regular medications as well as ASA scores and relevant comorbidities. Preoperative blood biochemistry will be recorded if known severe liver

function tests prevent lignocaine administration, at which point the patient will be excluded from the trial.

Choice of the amount of anaesthetic agent and post-operative analgesia will be at the discretion of the anaesthetist.

Fluid management will be at the discretion of the anaesthetist.

Study Endpoints

Primary Outcome:
1) Time to eye opening (using propofol +/- study drug only)

Efficacy endpoints
- 1) Endoscopy conditions
    - Global satisfaction items of the Clinician Satisfaction with Sedation Instrument (see below)
    - Modified Observer Assessment of Alertness/Sedation at time of endoscope insertion (see below)
- 2) Time for discharge from recovery

CLINICIAN SATISFACTION WITH SEDATION INSTRUMENT (CSSI) - Items 17-21 Global satisfaction

		Very Satisfied	Satisfied	Somewhat Satisfied	Neither Satisfied Nor Dissatisfied	Somewhat Dissatisfied	Dissatisfied	Very Dissatisfied
1.	**Your overall satisfaction with the procedure**	1	2	3	4	5	6	**7**
2.	**Your overall satisfaction with the sedation part of the procedure**	1	2	3	4	5	6	**7**
3.	**Patient's cooperation level**	1	2	3	4	5	6	**7**
4.	**Overall ease of the procedure**	1	2	3	4	5	6	**7**
5.	**Method of sedation compared with other methods of sedation**	**1**	**2**	**3**	**4**	**5**	**6**	**7**

Vargo J, Howard K, Petrillo J, Scott J, Revicki DA. Development and validation of the patient and clinician sedation satisfaction index for colonoscopy and upper endoscopy. *Clin Gastroenterol Hepatol* 2009; **7**(2): 156-62.

Target sedation: 3-4 of the Modified Observer Assessment of Alertness/Sedation. Scale MOAA/S Scale

0 = Unresponsive to deep stimuli
1= Unresponsive to shaking
2= responsive to shaking
3=responsive to loud verbal commands
4= lethargic response to normal verbal commands
5= responsive and alert
6= agitated

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Safety endpoints

1) Local and systemic complications from study drug administration
2) Episodes of oxygen desaturation as measured by pulse oximetry
    - Number of desaturation events
    - Nadir of oxygen desaturation
    - Duration of any desaturations
3) Observations: BP, HR, SpO2, pain scores until patient leaves PACU
4) Readmission within 24 hours post procedure and length of hospital stay

Sample Size and Statistical Analysis

Statistical analysis will be done by Prof Paul Myles. The sample size is chosen to provide sufficient information to determine a statistically significant difference between groups.

We plan to report and publish this trial according to the CONSORT 2010 statement.[1]

Data collection and management

Data will be stored according to Victorian privacy principles. De-identified electronic study data will be collected and managed using REDCap electronic data capture tools hosted and stored by Alfred Health (indefinitely). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.[2,3]

References

1. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016; **355**: i5239.
2. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; **95**: 103208.

3. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**(2): 377-81.

Safety Monitoring Plan: ADVERSE EVENTS (AE)

An **adverse event** is any adverse change in health or **side effect** that occurs in a person who participates in a clinical trial while the patient is receiving the treatment (study medication, application of the study device, etc.) or within a previously specified period of time after the treatment has been completed.

"An unfavourable or unintended sign, symptom, reaction, or disease that is associated in time with the use of an investigational drug"

SERIOUS ADVERSE EVENTS (SAE)

Serious adverse events are serious adverse events judged to be related to therapy.

An event should be considered **unexpected** if the nature, severity or frequency of that event is not consistent with the information in the current Australian Product Information.

- The event must be a SAE.
- There must be a certain degree of probability that the event is an adverse reaction to the administered drug.
- The adverse reaction must be unexpected. This means not foreseen in the Summary of Product Characteristics (SPC) in the case of an authorised medicinal product.
- (SUSARs) are serious adverse events judged to be related to therapy.

It is expected that nearly all participants will have adverse experiences given their comorbidity and extent of surgery, and so we ask investigators to limit adverse event reporting to those not anticipated with these factors in mind. However, if there is uncertainty that cannot be resolved with the local site investigator then such events should be noted

HOW TO REPORT ADVERSE EVENT IN LIGNOCAINE IN GASTROSCOPY – LIG TRIAL

Clinical investigators and ultimately the protocol Principal Investigator (PI) have the primary responsibility for AE identification, documentation, grading and assignment of attribution

1. Is this related to the study medication

2. Is this unexpected
3. Have you spoken with the investigator
4. Has this information been collected anywhere in the CRF or anaesthetic record
5. Is this a common event
6. Have you referred to procedure manual / Investigational product information

The intensity of each event should be assigned to one of the following categories:

- Mild - an adverse events which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate - an adverse events which is sufficiently discomforting to interfere with normal everyday activities.
- Severe - an adverse events which is incapacitating and prevents normal everyday activities and/or requires therapeutic intervention (i.e. use of a prescription drug or hospitalisation).

NOTE a severe adverse event is not necessarily a serious adverse event

Adverse events categorized as "serious" and related to treatment (results in death, illness requiring hospitalization, events deemed life-threatening, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or medical important condition) must be reported to the regulatory authorities immediately, whereas non-serious adverse events are merely documented in the annual summary sent to the regulatory authority

WHEN TO REPORT ADVERSE EVENTS

- AE
  - Baseline, Day of Surgery, Day of Discharge
  - Documented in CRF

- SAE
  - Reportable within 72 hours of drug administration
  - Source documentation
  - Event reporting page
  - Forward to ethics, DMC

- SUSAR
  - Urgent report within 24 hours of drug administration

EXAMPLES OF REPORTABLE ADVERSE EVENTS

It is important to note that all information collected in the CRF is NOT to be reported as an adverse event. All CRF data collected has been identified as an important event for the study. Therefore any item collected should not be reported a second time.