Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 6 Issue 8 August 2023

Research Article

# Randomised Controlled Trial (Feasibility Study) of Prophylactic Pyloric Balloon Dilatation During Ivor Lewis Esophagectomy to Prevent Delayed Gastric Emptying

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**Received:** May 08, 2023

**Published:** July 12, 2023



## Abstract

Early delayed gastric emptying (DGE) occurs in up to 37% of patients following esophagectomy. This can contribute to increased anastomotic leak and respiratory infection rates. Although the treatment of DGE in the form of pyloric balloon dilatation (PBD) post-operatively is well established, there is no consensus on the optimal approach in the prevention of DGE. The ultimate aim is to carry out a randomised control trial to determine the efficacy of prophylactic PBD in the prevention of DGE following esophagectomy. This manuscript details the protocol, recruitment strategy and potential timeline for a feasibility study addressing this. We detail the rationale, objectives, design and methods of this study. Patients will be recruited over a six-month period and randomised to either a control group (no intervention) or a treatment group (prophylactic PBD).

**Keywords:** Delayed Gastric Emptying (DGE); Pyloric Balloon Dilatation (PBD); Stomach

## Introduction

### Background

Ivor Lewis first described his technique in performing open esophagectomy (ILGO) in the Hunterian lecture in 1946 [1]. The Ivor Lewis gastro-esophagectomy is a complex operation that is performed to treat cancer of the esophagus (food pipe) whereby most of the esophagus and upper stomach are removed and the remaining stomach (conduit) is brought into the chest and joined to the remaining esophagus. Since then, it has been performed in hybrid (laparoscopic abdomen and open chest), and completely minimally invasive (either laparoscopic or robotic) techniques. 5-year survival was initially lower than 10% [2]. As survival figures have improved [3], more focus on short term and long-term morbidity has emerged.

Delayed gastric emptying (DGE) is one of these complications and has an incidence of up to 37% [4].

DGE symptoms are multiple and range from vomiting, dysphagia to solids, regurgitation to malnutrition [3]. It can lead to multiple complications including anastomotic leak, aspiration pneumonia, malnutrition and longer hospital stay. There are multiple discussions regarding the definition of DGE. Although some groups have introduced definitions [5], there still remains a disagreement in a clear consensus. In Derriford, early DGE is defined as 24-hour

nasogastric output greater than 50% of total oral fluid intake in that period. It is also defined by chest x-ray when the conduit (stomach joining esophagus) expands to greater than 50% of the width of right chest (hemi-thorax) at day four post ILGO. Objective diagnosis can be achieved by radioactive $TC^{99m}$ labelled meal [6]. It is not fully understood what causes of DGE.

Dysfunction of gastric motility, as the stomach is mobilised into the chest, and increased pyloric tone secondary to division of the vagus nerve have all been proposed as mechanisms leading to DGE. Reported risk factors for DGE include respiratory comorbidity, anastomotic leak (leak from the operative join between remaining esophagus and stomach) and post-operative respiratory complications [7].

Mechanical complications such as development of para-conduit hernia (parts of the bowel getting into the chest next to the conduit, causing a squashing effect) can also cause DGE.

Management and prevention of DGE has been divided into pharmacological, endoscopic and surgical (Diagram 1). It is however difficult as the complete pathophysiology of the problem is not fully understood.

Prokinetic agents such as erythromycin and domperidone, which increase the contraction of the stomach to empty faster have been used [3] to treat DGE. Endoscopic management in the form of pyloric balloon dilatation (stretching)using 30 mm rather than 20 mm has also been shown as a mode of treatment [8].

Post-operative surgical treatment includes treatment of para-conduit hernias. Prevention however has been more challenging. Intra-operative endoscopic botulinum injection into the pylorus showed no significant reduction in incidence of DGE [9]. Techniques such as finger fracture (breaking the pyloric muscle by hand and can only be done in open procedure), Heinke-Mikulicz pyloroplasty and pyloromytomy have shown no significant difference in reduction of DGE between the intervention and control groups [10,11]. Furthermore, they can also lead to other complications including bile reflux and closure site leak [10,11]. Preoperative endoscopic pyloric balloon dilatation with 20 mm has been shown to decrease incidence of DGE (only 18.3 % of the intervention group developed DGE compared to 37.5% in the non-intervention group) [12]. This however was a cohort study, and the main issue was that the intervention group had 115 patients whilst the non-dilatation group had 24 patients (tumour could not be passed with the scope). There aren't currently any published randomised control trials that looked at intra-operative endoscopic pyloric dilatation and how this relates to incidence of DGE.

University hospital Plymouth (UHP) nationally has the fourth highest number of esophagectomies annually. There has been extensive work done on DGE in the unit. In the previous project done at the unit, a definition of DGE has been achieved [9]. Every esophagectomy patient routinely has an intra-op endoscopy as part of the procedure. In the unit the forementioned study compared intra-op pyloric botox injection versus control group. The unit carries out routine pyloric dilatation as mainstay treatment for if the patient develops DGE after surgery. A cohort study had been done already been published by another group which confirmed the safety of intra-op balloon dilatation [12], the next natural step for the unit is to carry out a randomised control trial comparing intra-operative balloon dilatation and standard practice.

## Rationale for current study

Pyloric balloon dilatation is on the of the mainstay managements postoperatively of DGE. Systematic reviews and meta-analysis have shown there is no significant effect of other pre-operative/ intra-operative interventions on DGE, including botox and pyloroplasty. Pre-operative management with balloon dilatation has been shown in a cohort study to have a significant effect on reduction of DGE. By carrying out this RCT, the purpose is to seek increase in our knowledge in identifying a preventive measure of DGE which is practical and applicable.

## Participant and public involvement

Patients undergoing esophagectomy in the surgical ward currently were told about the intention of this study. They were shown the information leaflet and consent forms. They gave valuable feedback regarding where things can be corrected to be understood by the patient population. After an informal discussion, very informative input was put into the consenting process, including timing and modes of communication (e.g. clinic or over the phone).

## Methods

### Study objectives

### Primary objectives

As a feasibility study, the objectives will be to ascertain the following:

- Number of patients approached
- Number of patients who agreed to be randomised
- Number of patients successfully randomised
- Number of patients who dropped out
- Successful measurement of outcome measures

### Secondary objectives

Assessment of process and procedure of study such as:

- Blinding of the research team
- Completion of quality-of-life questionnaire by patients

### Outcome measures

- Rate of delayed gastric emptying
- Rate of anastomotic leak
- Rate of pneumonia

## Study design and methods

Patients will be randomised to prophylactic PBD or control group (no pyloric intervention). Patients routinely have endoscopy on the day of ILGO. All patients will undergo this with either balloon dilatation or no pyloric intervention. Patients will be blinded to this. The definition of early DGE according to our unit is 24-hour nasogastric output greater than 50% of total oral fluid intake in that period and conduit dilation greater than 50% of the right hemi-thorax at day four post ILGO. Outcomes will be assessed at 2 weeks and 3 months.

Derriford Hospital carries out 5-8 esophagectomies/month, meaning 30-48 patients in 6 months. With an aim of 80% recruitment, we will recruit at least 24 patients for the study.

### Study participants

### Screening procedures

All patients diagnosed with esophageal cancer are appropriately investigated to ascertain whether they are candidates for surgery. This includes assessment of fitness (please refer to Appendix regarding flow of care). It is during this process that they will be screened for inclusion and exclusion criteria.

### Inclusion criteria

All patients over the age of 18 undergoing Ivor Lewis esophagectomy in Derriford.

### Exclusion criteria

The participants may not enter the study if any of the following apply:

- Patient declined to participate.
- Impassable stricture at endoscopy.
- Patient is unable to give consent.

### Withdrawal criteria

It is always within the remit of the physician responsible for a participant to withdraw a participant from a trial for appropriate medical reasons, be that individual adverse events or new information gained about a treatment.

### Patient's decision

A patient is allowed to withdraw at any point. They can contact any member of the research team at any point to do so. The team member must identify whether the patient wants to withdraw from the whole study or particular aspects of it.

### Investigator decision

It should always be explained to the patient why their participation in the trial is terminated. Reasons for this will include:

- Serious adverse effects
- Increased risk to patient (including impassable tumour)

The data is pseudonymised with participants being given a unique identifier and a link held separately by the chief investigator. Once the patient withdraws from the study, the data collected at by this point may be retained and used. If the patient however does not wish for this to be used, then this will be respected.

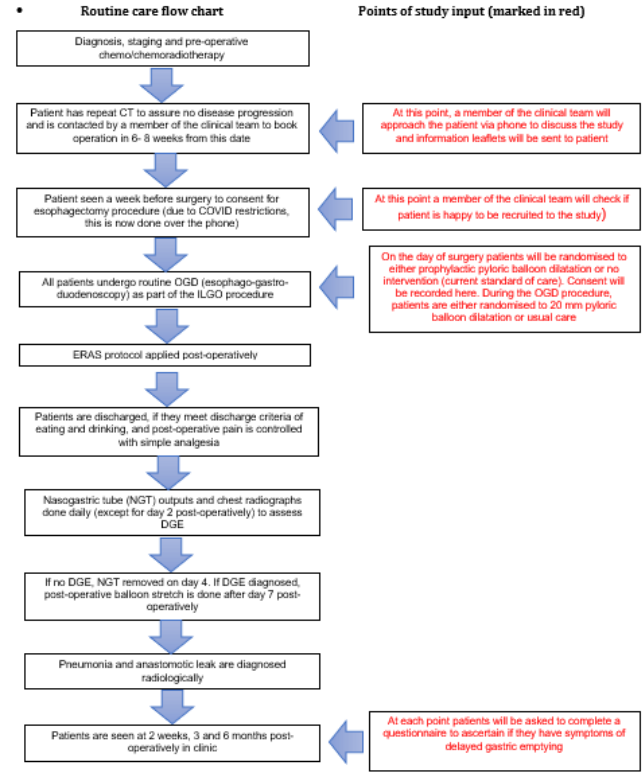


**Figure 1:** Study flow chart.

## Study procedures and interventions

### Recruitment

Usual care of patients is to contact them after the end of chemotherapy regarding the operation. This is done by phone. All patients who are eligible for ILGO at Derriford hospital will be approached. At this point, a member of the clinical team will phone the patient to introduce the idea of the study. If the patient is interested, the participation leaflets will be sent with the rest of the operation information. The patient is then given a chance to review these for 6-8 weeks. A week before the operation, the patient is routinely phoned to discuss the details of it. At this point, another opportunity is given to discuss the study with the patient after they've read the leaflets and thought about it for the past 6-8 weeks and whether they are still interested. On the day of the operation, the patient is seen face to face by a member of the clinical team to discuss the study and answer any further questions they have. If still interested, they will be requested to sign the consent forms at this point. Patients who are interested will have the study explained to them, addressing both their ideas, concerns and expectations and how the study falls within the remit of the whole operation. Derriford Hospital carries out between 5-8 esophagectomies a month. In a 6-month period, this will come to 30-48 patients. With 80% recruitment rate, the aim of the study is to recruit at least 24 patients.

### Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time of 6-8 weeks is allowed for consideration (please see above).

Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Patients who meet the study criteria will be approached by a member of the clinical team in the outpatient clinic

### Study assessments/interventions

The study flow chart (Figure 2) highlights how the study will be conducted to fit into normal patient care pathway. We will aim to enrol at least 24 patients undergoing Ivor Lewis esophagectomy. Patients will undergo 1:1 randomisation to prophylactic PBD or usual care (no pyloric intervention) using the sealed envelope software. Patients routinely have endoscopy on the day of ILO. All patients will undergo this with either balloon dilatation or no pyloric intervention. Both participant and the member of the research team analysing the data will be blinded. To ensure this the operation note will include the esophagectomy which is required for assessment of the note. The endoscopy with or without dilatation section will be recorded on a separate sheet (and kept

in a sealed envelope in the notes) that will be anonymised to the patient and the research member reviewing the notes. This seal would only be broken if there is a clinical need to do so.

The definition of early DGE according to our unit is 24-hour nasogastric output greater than 50% of total oral fluid intake in that period and conduit dilation greater than 50% of the right hemi-thorax at day four post ILGO. Patients are usually in hospital for 8 days if they don't develop complications. DGE will be assessed during hospital stay. Furthermore, outcomes will be assessed at 2 weeks and 3 months.

## Definition of end of study

This is defined as the date of the last visit of the last participant undergoing the study. The sponsor will notify the REC, in writing, within 90 days of the end of the study.

| | Dec-21 | Jan-22 | Feb-22 | Mar-22 | Apr-22 |
|---|---|---|---|---|---|
| First interaction by phone and leaflets sent 01/12/22-15/01/22 | ■ | ■ | | | |
| Phone one-week before the operation 08/01/22 | | ■ | | | |
| Meet and sign consent form on day of operation 15/01/22 | | ■ | | | |
| Patient admission 15/01/22- 22/01/22 | | ■ | | | |
| Patient seen in clinic (2 weeks post op) 06/02/22 | | | ■ | | |
| Patient seen in clinic (3 months post op) 22/04/22 | | | | | ■ |

| | Dec-21 | Jan-22 | Feb-22 | Mar-22 | Apr-22 | May-22 | Jun-22 | Jul-22 | Aug-22 | Sep-22 | Oct-22 | Nov-22 | Dec-22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient recruitment 01/12/21-01/06/22 | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | | | | |
| Research team monthly meetings | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Inpatient admissions 15/01/22-15/07/22 | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | | | |
| 2 weeks follow-up 06/02/22-06/08/22 | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | | |
| 3 months follow-up 22/04/22-22/10/22 | | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | |
| Data analysis 22/10/22-01/11/22 | | | | | | | | | | | ■ | ■ | |
| Study write-up 01/11/22-15/11/22 | | | | | | | | | | | | ■ | |
| Submit for publication 15/11/22-01/12/22 | | | | | | | | | | | | ■ | ■ |

**Figure 2:** Gantt charts.

a) Showing the journey of a patient in December' 21.

b) Showing planned period of the study.

## Safety reporting

### Definitions of adverse events

### Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical study subject. In this study, the main adverse event would be perforation secondary to dilatation of the pylorus. This is a serious adverse event that potentially can be life threatening and will prolong patient hospitalisation. We will be using 20 mm balloons for dilatation. The risk of perforation is less than 1%.

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

### Non serious AEs

All such events, whether expected or not, should be recorded.

### Serious AEs

An SAE form should be completed and faxed to the Chief/ Principal Investigator within 24 hours. However, relapse and death due to esophageal cancer and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the name of REC and copied to the R&D Office where in the opinion of the Chief/Principal Investigator, the event was:

- 'related', i.e., resulted from the administration of any of the research procedures; and
- 'unexpected', i.e., an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief/Principal Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies.

Local investigators should report any SAEs as required by their Research Ethics Committee and Research and Development Office.

## Statistics

The number of participants

As this is a feasibility study, the recruitment will occur over 6 months. UHP carries out 5-8 esophagecotomies/month. With the aim of 80% recruitment, the aim would be to recruit 24-32 patients in this period.

## Sampling

As this a feasibility study, the sample size is to ascertain if this study can be practically implemented. Sample size for the full RCT will be calculated accordingly.

## Analysis of endpoints

This is referred to in section 2.1 for outcome measures.

## Ethical and regulatory compliance

### Ethics and HRA approval

The Chief Investigator has obtained approval from the Health Research Authority (HRA) and Research Ethics Committee (REC) on 01/12/21 (IRAS project ID: 287659). The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

### Confidentiality

To comply with the Data Protection legislation information must be collected and used fairly, stored safely and not disclosed to any unauthorised person. This applies to both manual and electronically held data.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and ensure the UK General

Data Protection Regulation (GDPR) in conjunction with the UK Data Protection Act 2018, which sets out the statutory requirements for the processing of personal data, is adhered to.

### Indemnity

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

### Sponsor

UHP will act as the main sponsor for this study assuming overall responsibility for the initiation and management of the trial. Delegated responsibilities maybe assigned to other relevant parties taking part in this study and appropriately documented.

### Monitoring

The study will be subject to monitoring by UHP under their remit as sponsor to ensure adherence to the UK Policy Framework for Health and Social Care Research (2017). All UHP studies will be initially monitored at 25 days (+/- 7 days) after R&D capability and capacity has been given. The subsequent level of monitoring will be determined by a risk assessment, or on a for cause basis. The study may also be audited/inspected by regulatory bodies to ensure compliance with national regulations.

### Study management

The day-to-day management of the study will be co-ordinated through the research fellow Mohamed Abdelrahman. The trial management group meeting will take place monthly to discuss recruitment of the study, any adverse events and future planning. This group will include at least David Chan, Mohamed Abdelrahman, Rosie Forbes, a representative of the clinical team and the study sponsor.

### Publication policy

It is proposed that the study team will prepare a plain English summary of the study results which will be sent to the study participants as soon as possible after the end of the study. The final results of the study will be disseminated via presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals.

## Discussion

This randomised controlled feasibility study comparing the use prophylactic PBD (intervention group) to no pyloric intervention (control group) has many strengths. Our systematic review and meta-analysis of observational studies concluded that prophylactic PBD significantly reduces the rates of DGE [13] thus improving outcomes of patients undergoing esophagectomy. There are currently no published randomised studies to examine this intervention. The intervention group will undergo a balloon dilatation of the pylorus during a routine endoscopy performed at the time of surgery. Patients will not know which arm they fall in as all patients undergo an endoscopy whilst anaesthetised for their esophagectomy. The documentation of this part of the procedure will be sealed in an envelope so both patients and relevant members of the research team will be blinded.

Results from this feasibility study will therefore provide valuable information prior to embarking on the main randomised controlled trial. The eligibility criteria are designed to enrol the right target population. Patients are excluded, when unable to give consent or have a complete endoscopy. The study design is achievable, and this has been granted ethical approval.

There are potential limitations with recruitment for this study. This includes inability to randomise patients who are found to have an obstructing tumour or disease progression. The use of a 30 mm balloon has been shown to be better than a 20 mm balloon at treating DGE post-operatively. Re-dilatation rate was 20% and 52.9% respectively [8]. The distance to the pylorus following esophagectomy is relatively shorter and therefore it can be reached with the shorter 30 mm achalasia balloon (90 cm in length). Preventing DGE with a 30 mm balloon is therefore not possible prior to resection unless it is performed following anastomosis which carries the risk of anastomotic disruption. There are no commercially available 30 mm balloon dilators long enough to reach the pylorus prior to resection. All observation studies carrying out prophylactic PBD used a 20 mm [12,14,15]. The success and safety of this was evident in all three studies.

## Conclusion

Prophylactic pyloric balloon dilatation is potentially a safe and effective procedure which can significantly improve outcomes in patients after an esophagectomy. This protocol describes details for the feasibility study to be carried out which will allow important learning points for the main randomised controlled trial.

## Acknowledgements

None.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study is sponsored by University Hospital Plymouth (Derriford Hospital). The hospital Research and Development department has been involved in preparation of the protocol and on ethics application.

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