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The PLUG Study – A Feasibility Study Investigating the Prevention of Post-operative Gastro-oesophageal Anastomotic Leaks with the use of a Surgical Adhesive, BioGlue

Submission date 29/06/2020	**Recruitment status** Stopped	[ ] Prospectively registered [X] Protocol
Registration date 30/06/2020	**Overall study status** Stopped	[ ] Statistical analysis plan [ ] Results
Last Edited 18/01/2023	**Condition category** Surgery	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims

For people who have cancer of the oesophagus (gullet), one possible treatment is surgery to remove the cancer. The operation is an oesophagectomy which involves the removal of the tumour and then re-connecting the stomach to the healthy oesophagus. A risk in this operation is a leak from that join. Surgeons are always working hard to reduce the risks of operations and we hope that our research can help to reduce the number of people who suffer a leak after their operation.

This research study will investigate whether a type of surgical glue (BioGlue) can be used for patients having surgery for cancer of the oesophagus (gullet). A risk of this sort of surgery is a leak from the join between the stomach and the oesophagus. If this occurs, it means people need to stay in hospital for treatment and can mean they become seriously unwell. This study is the first step to find out if a type of surgical glue can help reduce the number of patients who suffer a leak.

This study will assess how easy it is to use and make sure it is safe to use in this way. We hope that this study will allow us to take on a much bigger study to look further into the potential benefits of this technique.

Who can participate?

We will offer all patients who will have an oesophagectomy for oesophageal cancer the option of being involved.

What does the study involve?

Other than the use of the glue, all other parts of a patient's care will be the same as a patient who is not part of the trial. During the operation, the surgeon will apply the glue on top of the join they make between your stomach and oesophagus. It is important to understand that the glue will be applied in addition to (not instead of) the normal way of making the join. The application of the glue to the join will be video recorded and kept for study records. It is done

using the key-hole camera that the surgeons use to do the operation inside the body. Participants will not be identifiable from this recording and it will only be used for internal study purposes. Other than adding the glue during the operation, participants care will otherwise be identical to if they are not part of the study. If participants decide not to take part in the study, they will receive the normal high-quality care from their surgeon and the wider team in the hospital. This study will look at how feasible it is to carry out a large-scale study, in many different hospitals.

What are the possible benefits and risks of participating?
We believe that by using this glue in addition to the normal way of making the join, we may reduce the number of people who have a leak from the join between their stomach and oesophagus. We will use the information we get from this study to help plan a larger scale study in the future. At this point we do not know for certain if using the glue will cause a lower leak rate, a higher leak rate or have any effect on the leak rate at all. This study will help surgeons and patients decide whether the use of this glue is better or not.

The glue we are using has been used for many years in different areas of surgery (mainly surgery on the heart and blood vessels). We do not expect there to be any significant increased risk from the use of the glue, but there are some small risks from the glue:
• Inflammation directly as a result of the glue
• Allergy to the glue's ingredients
• Damage to the normal tissues around the join
• Possible transmission of infection from material of animal origin
The glue has been used since 1998 and is regulated and licensed for use in the alimentary tract (gut).

Where is the study run from?
Queen Alexandra Hospital (UK)

When is the study starting and how long is it expected to run for?
October 2018 to June 2023

Who is funding the study?
The study is funded by the Sponsor, Portsmouth Hospitals NHS Trust, who will meet the costs of the delivery of the study. The BioGlue and laparoscopic applicator tips are being provided by CryoLife Europe Ltd.

Who is the main contact?
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Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
272689

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 44683, IRAS 272689

Study information

Scientific Title
Feasibility study investigating the Prevention of post-operative gastro-oesophageal anastomotic Leaks with the Use of a surgical adhesive, BioGlue – the PLUG study: a single-arm study

Study objectives

1. Is it technically feasible to use BioGlue as an additional measure to supplement standard procedure in the creation of a gastro-oesophageal anastomosis in the context of a minimally invasive oesophagectomy?
2. Are there any additional complications observed as a result of using BioGlue?
3. What is the observed anastomotic leak rate in patients receiving BioGlue?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/01/2020, South Central – Berkshire B Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8226; berkshireb.rec@hra.nhs.uk), ref: 20/SC/0005

Study design
Non-randomised interventional feasibility study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Gastro-oesophageal surgery

Interventions
SUMMARY OF STUDY DESIGN
This is a feasibility study to assess the ease of use and safety of a surgical adhesive (BioGlue) to reinforce the surgical join (anastomosis) between stomach and oesophagus (gullet) following key hole removal of a cancer of the oesophagus (oesophagectomy). The study will be undertaken at a single centre, Queen Alexandra Hospital Portsmouth. It is a single arm intention to treat study where all participants will be offered/receive the intervention (there is no control group). Consecutive participants will be recruited up to a number of 30. Currently around 70 oesophagectomies are performed at our centre annually; and we expect recruitment to be completed within 12
months.

Participants will all have been booked for a minimally invasive oesophagectomy and meet inclusion/exclusion criteria. They will all have the same procedure with the addition of BioGlue to the anastomosis. They will all receive the same post-operative care and follow up as normal, with an additional check up with the research team 6 weeks after surgery.

STUDY PARTICIPANTS

All patients who are found to have operable oesophageal cancer during the study period will be screened against the eligibility criteria and offered to take part in the study. Patients will be recruited from specialist clinic following discussion at the Upper GI cancer multidisciplinary team meeting (MDT), at which point they will be introduced to the study and given the participant information sheet to read. All patients will have a pre-operative fitness assessment and key hole procedure to assess the stomach prior to surgery. Potential participants will have the opportunity to ask questions at any appointment or by contacting the research team directly. Consent will be taken on the day of
oesophagectomy.

ENROLMENT

On the day of oesophagectomy participants will be enrolled onto the study. The research team will ascertain that the patient has understood what the study involves before consenting them. If they agree to be included in this study, they will be asked to sign a consent form and a Case Report Form (CRF) with a Participant Study ID created at this point with a record made in the patient's notes and a standard letter to patient's GP.

STUDY ASSESSMENTS

Baseline information will be recorded on the case report form about the participant:
1. Age, gender and physical activity.
2. Weight, height and body mass index.
3. Medical history, medications and allergies.
4. Symptoms experienced and pre-operative investigation findings.

Intra-operative information recorded will include:
1. Date of surgery.
2. Length of operation.
3. Any difficulty in application of BioGlue; specifically, areas where it wasn't applied.
4. Intra-operative complications.
5. Any concerns about the viability of the stomach or anastomosis.
6. Any deviation from standard operating protocol.

INTERVENTION

The surgical procedure is called a minimally invasive oesophagectomy and is performed in routine fashion. It involves a key hole approach to the abdomen (tummy) where the stomach is fashioned into a tube called a gastric conduit, and a feeding tube into the small bowel is also placed through the abdominal (tummy) wall. The oesophagus (gullet) is then mobilised using a key hole approach through the chest, and the cancer removed. The gastric conduit is then anastomosed to the oesophagus in the chest. At this point the BioGlue will be applied to the outside of the anastomosis. The inside of the anastomosis is normally assessed using a telescope through the mouth at the end of the procedure.

FOLLOW UP

After surgery patients will be admitted to intensive care where they will be managed identically to patients who have not been included in the study. A standardised Enhanced Recovery Programme is followed for all patients who have an oesophagectomy. Decisions about change in care will be made by an appropriately experienced consultant surgeon Progression in the post-

operative phase will be based on the patient's clinical progression and blood tests. Imaging, such as CT scans, will be used as felt appropriate.
Up until the day of discharge all patients will have at least once daily clinical review by the surgical team. The majority of anastomotic leaks occur fairly early in the post-operative phase and almost all before discharge. Following discharge from hospital patients will be followed up with a phone call one week after discharge and then in the outpatient clinic at 2 and 6 weeks. In addition to normal post-operative follow up, participants in the study will all be seen at six-weeks following their surgery by the research team.

Intervention Type
Procedure/Surgery

Primary outcome measure
The primary outcome is to assess whether it is technically feasible to apply BioGlue to the gastro-oesophageal anastomosis during oesophagectomy. This will be assessed using qualitative measures by the Operating Surgeon applying the BioGlue. These will include an overall rating describing the ease of application and a structured questionnaire addressing potential problems with the use of application of the BioGlue or laparoscopic applicator tips. Any further issues raised by the Surgeon will also be documented.

Secondary outcome measures
Measured at least once daily with clinical review by the surgical team up until the day of discharge, unless otherwise stated:
1. Post-operative complications up to six weeks, graded with the Clavien-Dindo scale
2. Anastomotic leak rate
3. All-cause mortality up to 6 weeks follow up
4. Operative duration
5. Time to discharge from hospital
6. Unplanned return to ITU up to 6 weeks follow up
7. Unplanned return to theatre up to 6 weeks follow up
8. Unplanned return to surgical high care unit up to 6 weeks follow up
9. Acceptability of the product to the surgeons and the theatre team (assessed using qualitative methods)
10. Number of CT scans
11. Use of antibiotics (duration, indication and type)

Overall study start date
01/10/2018

Completion date
01/06/2023

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. NHS patients undergoing elective minimally invasive oesophagectomy for cancer
2. Aged 18 years and above
3. Able to provide informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 30; UK Sample Size: 30

Key exclusion criteria
Previous adverse reaction to BioGlue or one of its constituent ingredients

Date of first enrolment
01/03/2020

Date of final enrolment
01/01/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Queen Alexandra Hospital
Cosham
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Sponsor information

Organisation
Portsmouth Hospitals NHS Trust

Sponsor details

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Sponsor type
Hospital/treatment centre

Website
http://www.porthosp.nhs.uk/

ROR
https://ror.org/009fk3b63

Funder(s)

Funder type
Industry

Funder Name
Cryolife Europa Ltd.

Results and Publications

Publication and dissemination plan
The research findings will be disseminated:
• Locally via our annual R&I conference
• Nationally presented in Association of Upper Gastro-intestinal Surgeons of Great Britain and Ireland (AUGIS) and/or Association of Surgeon of Great Britain and Ireland (ASGBI)
• Internationally presented at European Society of Surgical Oncology (ESSO) conference
• Published in a reputable peer-reviewed surgical journal
• Lay summaries available on R&I website and sent directly to all participants

Intention to publish date
01/06/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Portsmouth Hospitals NHS trust where it will be stored on internal servers. The type of data that will be available after de-identification will be text, tables, figures. The

data will be available at the beginning and ending 12 months after the article publication. Data will be available to researchers who provide a sound proposal – these should be directed to research.office@porthosp.nhs.uk for access and requestors will be to sign a data sharing agreement.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v2	20/01/2020	30/06/2020	No	Yes
Protocol file	version v2.0	20/01/2020	30/06/2020	No	No
HRA research summary			28/06/2023	No	No