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Prevention of heart and lung complications by using simvastatin in patients undergoing surgery for removal of food pipe

Submission date
11/10/2016

Recruitment status
No longer recruiting

Registration date
11/11/2016

Overall study status
Completed

Last Edited
10/07/2025

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
One lung ventilation is an anaesthetic technique used in common surgeries like oesophagectomy, lobectomy and pneumonectomy and is associated with pulmonary (lung) complications including acute respiratory distress syndrome (ARDS) and cardiac (heart) complications after surgery. Heart and lung complications account for up to 50% of complications requiring admissions to Intensive Care Units (ICUs). The risk of dying is significantly increased in these patients when compared to patients who do not suffer these complications. There is also a long-term impact as these patients have physical and mental health issues. There is also a reduced rate of return to employment and an increase in healthcare costs, as the ICU is an expensive and limited resource and a bed in ICU costs up to £1500. These patients also have a higher rate of healthcare contacts after discharge. Simvastatin belongs to a group of medications that are used to reduce fat levels in the blood. Simvastatin has also been shown to reduce inflammation and cell damage. In various studies it has been shown to reduce the rates of progression of severe infection, death from sepsis, and ICU admissions. In a small study simvastatin was found to reduce inflammation in the lungs and reduce the rates of heart, lung and infective complications. Development of these complications is associated with a significantly worse outcome including increased mortality (death rate), readmission to ICU, and increased ICU and hospital stay. The aim of this study is to find out whether treatment with simvastatin for four days before surgery and up to 7 days after surgery prevents cardiac and respiratory complications in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy.

Who can participate?
Patients aged 18 or over undergoing oesophagectomy, lobectomy or pneumonectomy

What does the study involve?
Participants are randomly allocated to take either once daily simvastatin or placebo (dummy) tablets for 3 days before the operation, on the morning of surgery and for 7 days after. All participants are followed up for 90 days. Complications, quality of life, costs and side effects are assessed, and blood and urine samples are taken.

What are the possible benefits and risks of participating?
Simvastatin is a cheap drug and costs less than £5 for the proposed treatment. If simvastatin is proven to be beneficial, this study may improve both patient outcomes and reduce costs to the NHS.

Where is the study run from?
1. Belfast Health and Social Care Trust (UK)
2. Royal Liverpool University Hospital (UK)
3. Birmingham Heartlands Hospital (UK)
4. Leicester Royal Infirmary Hospital (UK)
5. James Cook University Hospital (UK)

When is the study starting and how long is it expected to run for?
January 2016 to January 2021

Who is funding the study?
Health & Social Care Services R&D Award

Who is the main contact?
Dr Murali Shyamsundar

Contact information

Type(s)
Scientific

Contact name
Dr Murali Shyamsundar

Contact details
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Additional identifiers

EudraCT/CTIS number
2015-004424-65

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

15085MS-AS

Study information

Scientific Title
Prevention of post-operative complications by using HMG-CoA reductase inhibitor in patients undergoing oesophagectomy: a multicentre, randomised, double-blind, placebo-controlled trial

Acronym
Prevention HARP-2

Study objectives
Simvastatin 80 mg when compared to placebo will reduce cardiac and pulmonary complications in patients undergoing oesophagectomy, lobectomy or pneumonectomy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central - Berkshire Research Ethics Committee, 08/04/2016, ref: 16/SC/0152

Study design
Prospective randomized double-blind placebo-controlled Phase II multi-centre trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

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

Health condition(s) or problem(s) studied
Cardiac and respiratory complications following oesophagectomy, lobectomy or pneumonectomy

Interventions
Patients will be randomised to receive either once daily simvastatin 80mg (as two 40mg tablets) or two matched placebo tablets administered enterally. Patients will self-administer the medication orally for 3 days preoperatively, on the morning of surgery and postoperatively the study drug will be administered for 7 days by the ward staff.

Pre-screening visit – will look at potential patients
Baseline Visit – ICF, bloods and urine, randomisation and treatment allocation
Pre-admission (surgery) – telephone check for adverse events/serious adverse events
Day 0 - surgery, study drug, bloods and urine
Days 1–7 – bloods and urine, clinical outcome/safety assessments
Days 8–28 – or until hospital discharge, clinical outcome/safety assessments
Day 90 follow-up – survival status, HE assessments

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Simvastatin

Primary outcome measure
Composite endpoint of the incidence of acute respiratory distress syndrome (ARDS) defined according to the Berlin definition, post-operative pulmonary complications (PPC) as defined by Melbourne group scale, and myocardial infarction as defined by ischaemic chest pain, ECG changes and a raise in plasma troponin and also by myocardial ischaemia post non-cardiac surgery (MINS) criteria during the first 7 days post-operatively.

Secondary outcome measures
Clinical outcomes:
1. Mortality at day 28 and 90
2. Ventilator free days (VFDs), defined as the number of days in the first 28 days following surgery that a patient is free from ventilator assistance for greater than 48 hours
3. ARDS, PPC and MI within 28 days of surgery or hospital discharge if earlier
4. Atrial fibrillation (AF) within 28 days of surgery or hospital discharge if earlier
5. Venous thromboembolism within 28 days of surgery or hospital discharge if earlier
6. Incidence and nature of any surgical complications will be recorded

Safety:
1. Creatine Kinase IU/L (CK) >10 times the upper limit of normal of local laboratory range, measured on day of surgery, day 3 and day 7 post-surgery
2. Alanine Aminotransferase/Aspartate Aminotransferase IU/L (ALT/AST) > 5 times the upper limit of normal of local laboratory range, measured on day of surgery, day 3 and day 7 post-surgery
3. Acute kidney injury defined according to KDIGO guidelines and using change from baseline serum creatinine, measured within 7 days of surgery
4. Adverse events (AEs), serious adverse events (SAEs) and occurrence of suspected unexpected serious adverse reactions (SUSARs)

Health Economic Outcomes
1. Health-related quality of life (HRQoL), measured using the EuroQoL-5 Dimension Questionnaire (5 level version) at randomisation and 90 days post-surgery
2. Resource use:
2.1. Length of Intensive Care Unit (ICU) stay (level 3 care)
2.2. Length of High Dependency Unit (HDU) stay (level 2 care)

2.3. Total length of hospital stay
2.4. Health service contacts up to 90 days post-surgery

Overall study start date
01/01/2016

Completion date
01/01/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 23/06/2017:
1. Adult patients ≥18 years of age undergoing elective oesophagectomy, lobectomy or pneumonectomy
2. Female subjects must be surgically sterile, or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 30 days after completion of treatment. A pregnancy test measured by urine HCG in females with child-bearing potential will be performed at pre-operative assessment clinic

Previous inclusion criteria:
1. Adult patients ≥18 years of age undergoing elective oesophagectomy
2. Female subjects must be surgically sterile, or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 30 days after completion of treatment. A pregnancy test measured by urine HCG in females with child-bearing potential will be performed at pre-operative assessment clinic

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
452

Total final enrolment
251

Key exclusion criteria
1. Age <18 years
2. Creatinine Kinase (CK) >5 times upper limit normal range in the local laboratory
3. Known active liver disease (Child’s Pugh score > 11) or abnormal liver function tests i.e. transaminases (AST or ALT) >3 times upper limit normal range in the local laboratory

4. Renal impairment (calculated creatinine clearance less than 30mL/minute)
5. Inability to take oral medication pre-operatively
6. Subject reported lactose intolerance
7. Participation in other intervention trials within 30 days
8. Current treatment with statins
9. Known hypersensitivity to the study medication
10. Previous adverse reaction to statins
11. Concomitant use of fibrates or other lipid-lowering therapy
12. Concomitant use of itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprivir, telaprevir, nefazodone, cyclosporine, danazol, amiodarone, amlodipine, verapamil or diltiazem, fusidic acid
13. Patients must be able to understand and give signed and dated informed consent indicating that they understand all the pertinent aspects of the trial

Date of first enrolment
21/11/2016

Date of final enrolment
28/09/2022

Locations

Countries of recruitment
England

Northern Ireland

United Kingdom

Study participating centre
Belfast Health and Social Care Trust
The Royal Victoria Hospital
Belfast
United Kingdom
BT12 6BA

Study participating centre
Royal Liverpool University Hospital
Prescot St
Liverpool
United Kingdom
L7 8XP

Study participating centre

Birmingham Heartlands Hospital
Bordesley Green E
Birmingham
United Kingdom
B9 5SS

Study participating centre
Leicester Royal Infirmary Hospital
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
James Cook University Hospital
Marton Rd
Middlesbrough
United Kingdom
TS4 3BW

Sponsor information

Organisation
Belfast Health and Social Care Trust

Sponsor details
Research Office
2nd Floor King Edward Building
Royal Hospitals
Grosvenor Road
Belfast
Northern Ireland
United Kingdom
BT12 6BA

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Government

Funder Name
Health & Social Care Services R&D Award

Results and Publications

Publication and dissemination plan
1. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (https://www.consort-statement.org).
2. The results of the trial will initially be reported to the trial collaborators as the success of the trial depends on the collaboration of doctors, nurses and researchers from across the study sites.
3. The findings will also be presented at national and international meetings with open access abstracts online e.g. the American Thoracic Society annual meeting. We also aim to publish the findings in high-quality peer-reviewed open access (via PubMed) journals in accordance with the open access policies proposed by the leading research funding bodies. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists.
4. Due to limited resources, it will be not be possible to provide each surviving patient with a personal copy of the results of the trial. However a lay person's summary of the principal findings of the results will be sent to all patients involved in the study at their request. In addition a lay person's summary will be sent to local and national patient support and liaison groups (e.g. CritPaL, hospital patient groups). A report of the study findings will be sent to the INVOLVE registry. Where appropriate, research details will also be posted on institutional websites available to the general public. In addition, the most significant results will be communicated to the public through press releases.

Intention to publish date
01/01/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Murali Shyamsundar.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		18/12/2018		Yes	No
Protocol file	version 10.0	22/03/2021	03/05/2023	No	No
HRA research summary			28/06/2023	No	No
Results article		08/07/2025	10/07/2025	Yes	No