ISRCTN18386427 https://doi.org/10.1186/ISRCTN18386427

The effect of sildenafil (REVATIO®) on post cardiac surgery acute kidney injury

Submission date
10/08/2015

Recruitment status
No longer recruiting

Registration date
01/10/2015

Overall study status
Completed

Last Edited
07/11/2023

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol

Background and study aims
Acute kidney injury (AKI) is sudden and severe damage to the kidneys that stops them working properly. AKI is a common complication for patients who are having heart surgery; it can affect more than 30% of such patients making them ten times more likely to die after their surgery. . Despite many decades of research into kidney injury there is no known effective treatment. The drug sildenafil, commonly known as Viagra, has been shown to protect the heart. The aim of this trial is to find out whether this drug can also provide protection for the kidneys and can prevent heart surgery patients from developing AKI.

Who can participate?
Adult heart surgery patients at risk of developing AKI.

What does the study involve?
Participants are randomly split into two groups, a control group who are given a glucose solution which acts as a placebo (inactive medication) and an experimental group who are given sildenafil. The participants are put on a drip containing the drug or the placebo 20 minutes before undergoing heart surgery. They have their urine tested at the start of the study and after 24 hours, as well as blood tests every day for a week to test whether signs of AKI can be found.

What are the possible benefits and risks of participating?
There are no direct benefits of participating, although giving sildenafil may help to protect the kidneys during the operation. Risks of participating are minimal, including general side effects from the drug given and risks of pain, bruising or infection from blood tests.

Where is the study run from?
Glenfield Hospital (UK)

When is the study starting and how long is it expected to run for?
June 2015 to July 2018

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
1. Mrs Tracy Kumar (Public)
2. Professor Gavin Murphy (Scientific)

Contact information

Type(s)
Public

Contact name
Mrs Tracy Kumar

Contact details
University of Leicester
Department of Cardiovascular Sciences
Clinical Sciences Wing
Glenfield Hospital
Leicester
United Kingdom
LE3 9QP

Type(s)
Scientific

Contact name
Prof Gavin Murphy

Contact details
University of Leicester
Department of Cardiovascular Sciences
Clinical Sciences Wing
Glenfield Hospital
Leicester
United Kingdom
LE3 9QP

Additional identifiers

Clinical Trials Information System (CTIS)
2015-003259-24

Protocol serial number
0360

Study information

Scientific Title
The effect of sildenafil (REVatio®), a PDE-5 inhibitor, on post cardiac surgery acute kidney injury: a randomised, placebo-controlled phase IIb clinical trial: The REVAKI-2 Trial

Acronym
REVAKI 2

Study objectives
1. Primary Hypothesis:
1.1 Postoperative AKI, defined as the rise in serum creatinine from baseline, will be less in cardiac surgery patients identified as being at increased risk of developing AKI preoperatively, by the administration of sildenafil, a PDE-5 inhibitor (Revatio®, Pfizer Inc).
2. Secondary hypothesis:
2.1. The frequency of postoperative AKI, as defined by KDIGO criteria will be reduced in high risk patients undergoing cardiac surgery with cardiopulmonary bypass by the administration of sildenafil
2.2. Sildenafil will have additional important organ protection effects for the heart and lung.
2.3. The effects of sildenafil will be mediated via inhibition of platelet, leucocyte and endothelial cell activation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Yorkshire & The Humber - Leeds East Research Ethics Committee, 07/12/2015, REC ref: 15/YH /0489

Primary study design
Interventional

Study design
Single-centre double-blinded parallel group randomized controlled trial

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Acute Kidney Injury

Interventions
Participants are randomly allocated into a control group and an experimental group. Sildenafil or glucose (placebo) will be given intravenously as a bolus dose then infusion. Sildenafil 10mg (made up to 15ml with glucose) over 20 minutes starting just prior to initiation of cardiopulmonary bypass followed by a continuous infusion intravenously of 2.5mg (made up to 50ml) over 2 hours. Placebo, glucose 15ml over 20 minutes starting just prior to initiation of cardiopulmonary bypass followed by a continuous infusion intravenously of 50ml over 2 hours.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)

Sildenafil

Primary outcome(s)
Serum creatinine measured from daily blood tests for up to 7 days post-surgery or discharge if earlier.

Key secondary outcome(s)
Current:
1. Acute Kidney Injury (AKI) Defined according to the KDIGO criteria defined as a rise in serum creatinine of >26µmol.l-1 within 48 hours or a doubling of the serum creatinine within 7 days of surgery. Serum creatinine measured at baseline, return from theatre, 6-12 hours post op, 24, 48, 72, 96, day 5, day 6 (or discharge), day 7 (or discharge) and 6 weeks
2. Changes in biochemical markers of renal injury and dysfunction (urine neutrophil gelatinase-associated lipocalin (NGAL)), and myocardial injury (serum troponin), measured at baseline, 6-12 hours post-op, and 48 hours post-op
3. Acute lung injury, low cardiac output, acute brain injury, acute liver or gut injury, sepsis syndrome, death. As per MOD Score including patient follow ups at ICU admission, 24, 48, 72 and 96 hours, day 5, day 6 (or discharge), day 7 (or discharge) and 6 weeks
4. Multiple Organ Dysfunction (MOD) Score at Pre op, ICU admission, 24, 48, 72 and 96 hours.
5. Length of ICU and hospital stay. Patient follow ups
6. Vital sign measurements and vasopressor use during and after drug administration.
7. Postoperative blood loss, transfusion of RBC and non RBC allogenic blood components. Patient follow ups post op
8. Expected adverse events other than those included in the primary endpoint. Patient follow ups
9. Endothelial function as measured by the reactive hyperemia peripheral arterial tonometry (RH-PAT) index. Baseline and 24 hours by ENDO-PAT
10. Laboratory measures of platelet, leucocyte and endothelial cell activation from blood samples pre op, 6-12 hours & 48 hours

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8. Expected adverse events other than those included in the primary endpoint. Patient follow ups
9. Endothelial function as measured by the reactive hyperemia peripheral arterial tonometry (RH-PAT) index. Baseline and 24 hours by ENDO-PAT
10. Laboratory measures of platelet, leucocyte and endothelial cell activation from blood samples pre op, 6-12 hours & 48 hours and tracheal aspirates pre op, 6-12 and 24 hours

Completion date
01/07/2018

Eligibility

Key inclusion criteria
Current:
1. Adult cardiac surgery patients (>18 years) undergoing cardiac surgery with cardiopulmonary bypass and cardioplegic arrest.
2. Identified as representing a high risk group for AKI using a modified AKI risk score; a predicted risk score of 22% equates to a positive predicted value for developing AKI of >55%.
3. Female subjects of childbearing potential are not to be pregnant (to be confirmed by urine human chorionic gonadotropin pregnancy test prior to dosing). Women are considered not to be of childbearing potential if they have been surgically sterilised (eg, tubal ligation, oophorectomy or hysterectomy) or are postmenopausal in the absence of hormone replacement therapy and complete absence of menses for at least 24 consecutive months.
4. Able, in the opinion of the investigator, and willing to give informed consent.

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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
129

Key exclusion criteria
Current:
1. Emergency or salvage procedure
2. Ejection fraction <20%
3. CKD Stage 5, defined as eGFR<15ml/min (as per the Modified diet in Renal Disease formula) or renal replacement therapy.
4. Patients with a pre-existing sepsis or organ injury defined as documented sepsis, acute kidney injury, acute lung injury, myocardial infarction, low cardiac output, liver injury, stroke or

pancreatitis within 5 days of surgery.
5. Administration of potent CYP 3A4 inhibitors within 1 month prior to study participation (e.g. HIV protease inhibitors, imidazole antifungals and erythromycin,
6. Administration of nitrate medicines (e.g. glyceryl trinitrate) within 24 hours of surgery.
7. Patients allergic to any other PDE-5 Inhibitor.
8. Patients who are participating in another interventional clinical study.
9. Patients who have loss of vision in one eye due to non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether it is connected to previous PDE5 inhibitor exposure.
10. Any ongoing malignancy or prior malignancy that currently requires treatment.
11. Female subjects of childbearing potential are not to be pregnant.
12. Cardiac surgery patients (<18 years) undergoing cardiac surgery with cardiopulmonary bypass and cardioplegic arrest.
13. Severe hepatic impairment.
14. Severe hypotension (blood pressure < 90/50 mmHg) on the day prior to surgery.
15. Administration of the guanylate cyclase stimulators, such as riociguat.
16. Unable, in the opinion of the investigator, or unwilling to give informed consent.

Previous:
1. Emergency or salvage procedure
2. Ejection fraction <20%
3. CKD Stage 5, defined as eGFR<15ml/min (as per the Modified diet in Renal Disease formula) or renal replacement therapy.
4. Patients with a pre-existing sepsis or organ injury defined as documented sepsis, acute kidney injury, acute lung injury, myocardial infarction, low cardiac output, liver injury, stroke or pancreatitis within 5 days of surgery.
5. Administration of potent CYP 3A4 inhibitors within 1 month prior to study participation (e.g. HIV protease inhibitors, imidazole antifungals and erythromycin,
6. Administration of nitrate medicines (e.g. glyceryl trinitrate) within 24 hours of surgery.
7. Patients allergic to any other PDE-5 Inhibitor.
8. Patients who are participating in another interventional clinical study.
9. Patients who have loss of vision in one eye due to non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether it is connected to previous PDE5 inhibitor exposure.
10. Any ongoing malignancy or prior malignancy that currently requires treatment.
11. Female subjects of childbearing potential are not to be pregnant

Date of first enrolment
24/01/2016

Date of final enrolment
01/08/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

Glenfield Hospital
Department of Cardiovascular Sciences
Clinical Sciences Wing
Leicester
United Kingdom
LE3 9QP

Sponsor information

Organisation
University of Leicester (UK)

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/06/2020	16/04/2020	Yes	No
Protocol article		18/10/2018	17/08/2022	Yes	No
Basic results			23/06/2020	No	No
HRA research summary			28/06/2023	No	No
Other publications		21/07/2022	07/11/2023	Yes	No