

A randomised controlled trial to evaluate whether use of intrapleural urokinase aids the drainage of multi-septated pleural effusion compared to placebo

Submission date 24/04/2008	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 05/06/2008	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 20/09/2017	Condition category Cancer	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

<http://www.cancerhelp.org.uk/trials/trials-search/trial-looking-using-urokinase-help-drain-fluid-around-lung-time3-uk>

Contact information

Type(s)

Scientific

Contact name

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Contact details

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Additional identifiers

Protocol serial number

N/A

Study information

Scientific Title

Adjuvant urokinase in the treatment of malignant pleural effusion: The third Therapeutic Intervention in Malignant Effusion trial

Acronym

TIME3-UK

Study objectives

A randomised controlled trial to evaluate whether use of intrapleural urokinase improves breathlessness and decreases the proportion of patients requiring further pleural fluid drainage to control breathlessness in subjects with septated/loculated malignant pleural effusions who are undergoing talc pleurodesis, compared to placebo.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Oxfordshire Research Ethics Committee A, 20/03/2009, ref: 09/H0604/5

Study design

Multi-centre randomised controlled trial

Primary study design

Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Malignant pleural effusions

Interventions

Treatment (urokinase) arm: Intra-pleural urokinase (100,000 IU in 30 ml normal saline) administered 12 hourly for a total of 3 doses.

Placebo arm: Intra-pleural urokinase placebo (in 30 ml normal saline) administered 12 hourly for a total of 3 doses.

All patients suitable for talc pleurodesis will receive this treatment after pleural drainage facilitated by the trial medication. For any patient where there is a contraindication to the administration of intrapleural talc, an alternative pleurodesis agent may be used.

Total duration of follow-up: 12 months post-randomisation

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Urokinase

Primary outcome(s)

1. Breathlessness quantified from visual analogue scales. The primary outcome will be the change in mean daily visual analogue scale (VAS) score defining breathlessness over 28 days following randomisation. A daily VAS score will be obtained at a similar time each day to assess how breathless each patient has felt over the preceding 24 hours.

The minimum clinically significant changes in the VAS scores have been established based on pilot data from previous studies determining the improvement in breathlessness associated with complete pleural fluid drainage with a permanent indwelling catheter. These are used in the power calculations. VAS methodology has been shown to be robust and reproducible. Patients who are known to be unable to record VAS scales (particularly the visually impaired) will be excluded (see Participants - exclusion criteria).

Added 09/08/2016:

2. After adjuvant urokinase/placebo treatment, all patients will have a sterile 4 g talc slurry pleurodesis. Pleurodesis will be performed with talc graded to exclude majority of $<10\ \mu\text{m}$ particles to minimise toxicity. The hypothesis is that the urokinase treatment will improve pleural drainage such that subsequent pleurodesis is more effective.

To assess whether adjuvant urokinase has improved the efficacy rate of pleurodesis, the failure rate of pleurodesis will be defined by the need for further pleural intervention within 28 days of randomisation. Recurrence of pleural fluid on imaging (e.g., chest radiograph or ultrasound) which is not causing sufficient breathlessness/pain to require further drainage will not be deemed pleurodesis failure.

Key secondary outcome(s)

1. Radiographic improvement in the area of the pleural effusion (measured as the difference in the proportion of the ipsilateral hemithorax occupied by the pleural effusion opacity on chest radiograph) on day three (the day of pleurodesis)
2. Total volume of pleural fluid drained
3. The proportion of patients requiring a further pleural fluid drainage to control breathlessness at 3 months
4. Self reported health status ('quality of life'), quantified from standard questionnaires at each trial assessment: Chronic Respiratory Disease Questionnaire (CRDQ) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30)
5. Health care costs (from health care utilisation and cost utility analysis from EQ-5D)

Completion date

30/06/2014

Eligibility

Key inclusion criteria

1. Both males and females
2. A clinically confident diagnosis of pleural malignancy defined as:
 - 2.1 Histocytologically proven pleural malignancy, or
 - 2.2. Otherwise unexplained exudative pleural effusion in the context of histocytologically proven cancer elsewhere
2. A significant ($>25\%$ hemithorax area) multi-loculated or multi-septated pleural effusion

(residual effusion on chest radiograph despite the presence of a patent in-situ chest tube)

3. Malignant pleural effusion requiring drainage and pleurodesis for symptom control

4. Written informed consent

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Sex

All

Key exclusion criteria

1. Age <18 years
2. Expected survival <28 days
3. Previous pneumonectomy on the side of the effusion
4. Positive ipsilateral pleural fluid gram stain or bacterial culture in the previous month
5. Previously received intra-pleural fibrinolytic agents into this effusion
6. Known sensitivity to urokinase
7. Coincidental stroke, major haemorrhage or major trauma
8. Major surgery in the previous 5 days
9. Chylothorax
10. Total blood white cell count $<1.0 \times 10^9$
11. Patients who are pregnant or lactating
12. Irreversible bleeding diathesis or platelet count $<100 \times 10^9$
13. Irreversible visual impairment
14. Inability to give informed consent or comply with the protocol

Date of first enrolment

01/09/2009

Date of final enrolment

30/06/2014

Locations

Countries of recruitment

United Kingdom

England

Study participating centre

UKCRC Oxford Respiratory Trials Unit
Oxford
United Kingdom
OX3 7LJ

Sponsor information

Organisation

University of Oxford (UK)

ROR

<https://ror.org/052gg0110>

Funder(s)

Funder type

Government

Funder Name

Grant application submitted to the National Cancer Research Institute (NCRI) (UK). Decision pending as of 01/05/2008.

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	15/02/2018		Yes	No
HRA research summary			28/06/2023	No	No