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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

Registration date
05/06/2008

Overall study status
Completed

Last Edited
20/09/2017

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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

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Additional identifiers

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

Primary study design
Interventional

Study design
Multi-centre randomised controlled trial

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 µm 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 x 10^9
11. Patients who are pregnant or lactating
12. Irreversible bleeding diathesis or platelet count <100 x 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