Randomised Controlled Trial of Urokinase versus Placebo for Non-draining Malignant Pleural Effusion

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At a Glance Commentary

Scientific Knowledge on the Subject: Two previous trials of intrapleural fibrinolytics for malignant pleural effusion demonstrated a significant increase in pleural fluid drainage, lung re-expansion, a decrease in requirement for supplementary oxygen therapy but no difference in recurrence rate following pleurodesis in the first 30 days.

What this study adds to the field: In this randomized controlled trial of intrapleural urokinase versus placebo in 71 patients with non-draining malignant pleural effusion despite the presence of a patent chest tube, there was no difference in the key clinical outcomes of dyspnea or time to pleurodesis failure over 1 year. Alternative palliative measures should be used to relieve breathlessness in this patient group.

Abstract

Rationale: Patients with malignant pleural effusion (MPE) experience breathlessness, which is treated by drainage and pleurodesis. Incomplete drainage results in residual dyspnea and pleurodesis failure. Intrapleural fibrinolytics lyse septations within pleural fluid, improving drainage.

Objectives: To assess the effects of intrapleural urokinase on dyspnea and pleurodesis success in patients with non-draining malignant effusion.

Methods: Prospective double blind randomised trial; patients with non-draining effusion were randomly allocated 1:1 to intrapleural urokinase (100,000 IU three doses 12 hourly) or matched placebo.

Measurements: Co-primary outcome measures: dyspnea (average daily 100mm visual analogue scores over 28 days) and time to pleurodesis failure to 12 months. Secondary outcomes: survival, time in hospital and radiographic change.

Main results: 71 subjects randomised (36 received urokinase, 35 placebo) from 12 UK Centres. Baseline characteristics were similar between groups. There was no difference in mean dyspnea between groups (mean difference 3·8mm, 95% CI -12 to 4·4mm, p=0·36). Pleurodesis failure rates were similar (urokinase 13/35 (37%), placebo 11/34 (32%), adjusted hazard ratio 1·2, p=0·65). Urokinase was associated with a decreased effusion size on chest radiograph (adjusted relative improvement -

19% (95% CI -28 to -11%, p<0·001), reduced hospital stay (1·6 days (95% CI 1·0 to 2·6), p=0·049) and improved survival (69 days versus 48 days, p=0.026).

Conclusions: Use of intrapleural urokinase does not reduce dyspnea or improve pleurodesis success compared with placebo, and cannot be recommended as an adjunct to pleurodesis. Other palliative treatments should be used. Improvements in hospital stay, radiographic appearance and survival associated with urokinase require further evaluation.

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- ISRCTN (www.isrctn.com): 12852177
- EudraCT (https://eudract.ema.europa.eu): 2008-000586-26
- MREC (nih.gov.my/web/mrec/): 09/H0604/5

Introduction

Malignant pleural effusion (MPE) is common, affecting an estimated 200,000 patients in the UK and USA per year(1, 2), and causes disabling dyspnea(3). Standard treatment involves drainage via chest tube, followed by artificial synthesis of the pleural membranes (pleurodesis) to prevent recurrence(3). However, initial drainage may be incomplete resulting in persistent breathlessness and preventing effective pleurodesis. This is due to fibrinous adhesions within the pleural space, dividing the fluid into septations(4). Ultrasound images demonstrate intrapleural fibrinolytics lyse adhesions and improve drainage in MPE(5).

While fibrinolytics alone are of no value in pleural infection(6, 7), two small trials of intrapleural fibrinolytics for MPE suggest some benefit(8, 9). Okur et al. randomised 47 patients to either streptokinase or no treatment and demonstrated a significant increase in pleural fluid drainage and lung re-expansion, but no difference in recurrence rate following pleurodesis(9). Saydam, et al. conducted a randomised trial of streptokinase or saline in 40 patients with loculated MPE visible on computer tomography(8), demonstrating significantly increased drainage, a decrease in requirement for supplementary oxygen therapy, and a non-significant decrease in pleural fluid recurrence in the first month following streptokinase. However, no trial to date has assessed the utility of intrapleural fibrinolysis on clinically meaningful outcomes in this population.

This trial was conducted to assess the effect of adjunctive intrapleural urokinase on improving pleurodesis, addressing the key clinical outcomes of dyspnea and

pleurodesis success in patients with non-draining MPE. Some of the results of this study have previously been reported in the form of an abstract(10).

Methods

Study design

The third Therapeutic Intervention in Malignant Effusion Trial (TIME3) was a double-blind, placebo-controlled randomised trial recruiting in 12 British hospitals. Ethical and regulatory approval for the study was obtained from NRES South Central – Oxford A, UK before recruitment commenced and the trial was registered (ISRCTN: 12852177, EudraCT number: 2008-000586-26, MREC number: 09/H0604/5). The trial was overseen by a Trial Steering Committee that met annually, and by a Data Monitoring Committee.

Participants

Adult participants with a diagnosis of MPE with a patent, correctly sited chest tube inserted for dyspnea relief, and significant residual pleural fluid gave written informed consent prior to enrolment. The diagnosis was established by either histo-cytological proof of pleural malignancy, or a recurrent large pleural effusion in the context of histologically-proven cancer outside the pleural space. For inclusion, patients initially required >25% opacification of the hemithorax by residual fluid on chest radiograph, but this was altered in March 2011 to either: >15% opacification of the hemithorax on chest radiograph; or, >2cm loculated pleural fluid visible on ultrasound. This trial

modification was made in response to increasing use of thoracic ultrasound in clinical practise in UK and to improve study recruitment.

Exclusion criteria were: age <18 years, expected survival <28 days, known underlying trapped lung of sufficient severity that pleurodesis is futile, previous lobectomy or pneumonectomy on the side of the effusion, pleural infection, previous intrapleural fibrinolytics, known urokinase allergy, coincidental stroke, major haemorrhage or major trauma, major surgery in the previous 5 days, chylothorax, pregnancy, lactating mothers, irreversible bleeding diathesis or platelet count $<100*10^9$, irreversible visual impairment and inability to consent or comply with the protocol. Initially, patients with highly chemotherapy-responsive tumours, such as small-cell lung cancer were excluded unless the patient had already undergone chemotherapy, but this exclusion criterion was removed in March 2011.

Randomisation and masking

Patients were randomised in a 1:1 ratio to urokinase or matched identical placebo using minimisation, with a random component of 80%, using a telephone randomization service provided by the Medical Research Council Clinical Trials Unit, London. Code break was only available to the trial statistician and this was not required at any time during the trial. Minimisation criteria were histologic tissue type (mesothelioma versus non-mesothelioma), previous pleurodesis (yes or no), World Health Organisation (WHO) performance status (0-2 or 3/4) and recruiting centre(11).

Treating physicians, patients and outcome assessors were blinded to treatment allocation throughout the study.

Baseline assessments (day 0)

At baseline, patients completed a 100mm visual analogue scale (VAS) score assessing dyspnea over the preceding 24 hours. The VAS has previously been validated to assess dyspnea in pleural disease(12) and consists of a 100mm line anchored with “no breathlessness” at 0mm and “maximum possible breathlessness” at 100mm(13). Patients were asked to mark the line at a point representing their level of dyspnea. Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30)(14) and baseline demographic and treatment data were recorded.

Trial interventions

Three doses of urokinase (100,000 units) or exactly matched placebo vials were reconstituted in 20ml 0·9% saline and injected intrapleurally at 12 hourly intervals via the chest tube (days zero to one). Twenty-four hours following the last dose (day two), a chest radiograph was obtained and talc slurry pleurodesis performed with 4g sterile high grade talc (Novatech, France) following trial specific procedures based on the national British Thoracic Society treatment guidelines(3). Pleurodesis was performed regardless of ongoing fluid drainage volume and chest radiograph

appearance. The chest tube was removed once significant drainage (>150mls in each 24 hour period) had ceased.

All participants received treatment of the causative primary tumour in accordance with current guidelines and oncological advice.

Trial assessments

Patients were followed up for 12 months after randomization or until death. Patients completed VAS scores at the same time each day for 28 days and at the three, six and twelve month assessment points.

Data on pleurodesis failure, the EORTC QLQ-30 questionnaire, assessment of complications, and health care utilisation were measured at 28 days and three, six and 12 months. All adverse events (AEs) occurring within the first three days following randomisation were recorded.

Trial outcomes

Primary Outcomes

The two co-primary outcome measures were:

1. Mean daily dyspnea over the first 28 days post-enrolment measured by VAS. All patient completed VAS scores were measured by two independent researchers and the mean measurement used.

2. Time to pleurodesis failure, defined as symptomatic ipsilateral pleural fluid recurrence. This required one of the following, to ensure clinical applicability of the study result:
    - A further ipsilateral drainage procedure to control breathlessness; or
    - Symptomatic pleural fluid recurrence as determined by the physician caring for the patient where a further procedure was not conducted (for reasons including patient choice, futility or other medical reason (e.g. anticoagulation, poor performance status)).

Secondary Outcomes

Predetermined secondary outcomes were:

1. Radiographic change 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 two post randomisation. The chest radiograph pleural opacity was measured using a validated digital system as has been reported previously(6).
2. Total volume of pleural fluid drained post-randomisation.
3. All cause mortality to 12 months.
4. Length of hospital stay post randomisation.
5. Frequency of serious and non-serious adverse events.
6. Blood parameters including biochemical and full blood count analysis.

Statistical Methods

Data were analysed on an intention-to-treat basis, and all randomised patients in whom an outcome was available were included in the analysis. Analyses were pre-determined prior to data analysis and a full Statistical Analysis Plan was signed off prior to assessment of any data (full details available in the online supplement). Analyses were adjusted for minimisation criteria (performance status, mesothelioma and previous pleurodesis)(15). Stata version 12·1 was used (StataCorp. 2011).

The difference between treatment groups in mean daily dyspnea VAS score over 28 days was calculated using a mixed-effects linear regression model, to account for days with missing VAS scores (as an unbiased analysis which does not differentiate between scores missing due to patient death and those missing because the patient did not complete their VAS score on that day). Study day was modelled as a continuous variable using fractional polynomials and was included in the model as a random effect. The model adjusted for the baseline VAS score(16) to increase statistical precision.

Time to pleurodesis failure was analysed using a competing risk model, with death as the competing risk.

Mean change in area of pleural effusion on day two (after receipt of trial drug, but prior to pleurodesis) was calculated using a linear regression model, adjusting for baseline proportion.

Sample Size Calculation

For the pleurodesis outcome, a 32% pleurodesis failure rate in the urokinase group and an 80% failure rate in the placebo group was assumed. With 25% loss to follow

up (from expected mortality known in MPE), 68 patients were required, with 90% power, 5% significance level.

For the dyspnea outcome, power calculations based on pilot data from patients with MPE indicated 126 patients were needed to detect a 7mm difference in VAS for breathlessness (SD =11mm, 90% power, alpha =0·05, with 25% loss to FU), and therefore a recruitment target of 126 patients was chosen. Towards the end of recruitment, data published demonstrated the minimally important difference of the VAS score for dyspnea for patients with pleural effusion was 19mm (95% CI 14-24mm) (12), and using this new data, the sample size required to detect a clinically important difference in dyspnea would have been 40 patients.

Results

The trial CONSORT flow chart is presented in Figure 1. Seventy one patients were recruited from 12 UK hospitals between 1st September 2009 and 30st June 2014, with recruitment ending due to expiry of the placebo medication. 36 patients were randomised to urokinase and 35 to placebo, with the treatment groups well matched at baseline (table 1).

Change in VAS dyspnea scores

In both groups, baseline VAS score was 38mm (standard deviation (SD) 28mm in urokinase, 25mm in placebo) (table 1). Mean VAS dyspnea over 28 days was 39mm in the urokinase group and 35mm in the placebo group, equating to an average mean difference in VAS score over 28 days from baseline of 1·4mm (SD 20mm) in the urokinase and -3·2mm (SD 21mm) in the placebo groups respectively. There was no significant difference between the two groups (adjusted mean difference from baseline between groups -3·8mm, 95% CI -12 to 4·4mm, p=0·36) (Figure 2). Outcome data was missing in eight patients (three in urokinase group, five in placebo) due to the following reasons: baseline VAS score only (1); VAS booklets not returned (7). A total of 34 patients died during the first 28 days post randomisation (19 urokinase, 15 placebo).

There was no difference in the number of patients achieving a clinically significant decrease in VAS dyspnea (>=19mm) between the two groups (urokinase 13 patients, placebo 15 patients, p=0.09).

Pleurodesis success

There was no significant difference in time to pleurodesis failure, which occurred in 13/35 (37%) of patients receiving urokinase compared with 11/34 (32%) receiving placebo (adjusted hazard ratio 1·2, p=0·65) (Figure 3). Two patients were excluded from analysis due to death occurring within three days of randomisation (one in each treatment group).

All cause mortality up to 12 months

Death occurred by 12 months of follow up in 31/36 patients in the urokinase group and in all patients in the placebo group. Median time to death after randomisation was significantly more in the urokinase group, with median survival of 69 (IQR 24-123) days in the urokinase group and 48 (IQR 31-80) days in the placebo group (adjusted analysis for minimisation factors, p=0·026).

Radiographic changes

Chest radiographs at baseline and day two were available for 47 patients (26 urokinase, 21 placebo). In the urokinase group, size of effusion decreased, but in the placebo group there was no significant change (urokinase: 35% hemithroax opacification (SD 20) at enrolment, 23% (SD 15) at day two; placebo group: 42% (SD 21) at baseline and 44% (SD 24) at day two (adjusted analysis for baseline % opacification, mean difference, placebo vs urokinase -19%, 95% CI -28 to -11%, p≤0·001).

Hospital Stay

Patients receiving urokinase had a shorter length of hospital stay (measured as time from randomization to discharge in patients who survived hospital admission) mean length of stay =6·2 days (SD 2·7) versus 8·7 days (SD 6·5) in the placebo group (adjusted hazard ratio 1·6 days (95% CI 1·0 to 2·6), p=0·049).

Fluid Output

Data were available for 24/36 patients in the urokinase group and 19/35 patients in the placebo group. There was no significant difference in total pleural fluid drainage between the groups from randomisation to tube withdrawal, with a mean drainage volume of 358ml in the urokinase group (SD 644) and 257ml in the placebo group (SD 402, adjusted mean difference 169ml (95% CI -111 to 448ml) (p=0·24).

Change in blood parameters from baseline to day three

There was no difference in change in haemoglobin, prothrombin time or activated partial thromboplastin time (APTT) between the two groups from baseline to day three (see eTable 1). Platelet counts were higher in those treated with urokinase compared to placebo (adjusted difference 39 (95% CI 1·6 to 76, p=0·041).

Quality of Life

There was no difference in self-reported health status or overall quality of life between the groups at any time point (adjusted difference in health status 1·6%, (95% CI -8·6 to 12), p=0·76; adjusted difference in quality of life 7·4% (95% CI -3·2 to 18), p=0·18).

Adverse events

Six serious adverse events occurred. Two deaths occurred within days zero to three due to progression of underlying malignancy (one urokinase, one placebo), two pleural infections (one urokinase, one placebo), one chest tube wound dehiscence (placebo) and one post-pleurodesis chest pain delaying discharge (urokinase). No intrapleural haemorrhage occurred, and one patient (receiving placebo) experienced systemic (pelvic) bleeding.

Discussion

This randomised placebo controlled trial is the first to compare urokinase with placebo for treatment of septated MPE, and the first intrapleural fibrinolytic trial to assess clinically meaningful outcomes (dyspnea and pleurodesis). Our results demonstrate no improvement in dyspnea or pleurodesis success following intrapleural urokinase despite chest radiographic evidence of significant reduction in size of pleural effusion.

Study participants in our selected population had a high mortality, demonstrating that the septated MPE population is likely to represent advanced malignancy. This poor survival means that interventions requiring hospital admission, such as talc pleurodesis, should be carefully considered in this population.

We observed a small but statistically significant decrease in mortality in the urokinase group, although it should be noted that fibrinolytics are not recognised to have anti-tumour effects, mortality was a secondary outcome and there was an excess of patients with lung cancer in the placebo group. This study was conceived before the development of the LENT score for prognostication in patients with MPEs so data was not collected to enable us to compare baseline prognosis between the groups(17). Neither of the previous randomised studies of intrapleural fibrinolytics in MPE reported mortality outcomes(8, 9), however this potential effect should be subject to further studies.

Urokinase was associated with a decrease in hospital stay compared to placebo, despite having no effect on dyspnea or fluid output, and in the presence of improved chest radiograph appearance in the urokinase group. The reasons for shortened hospital stay using urokinase are not clear, and require further investigation.

Our results support the findings of Okur, et al and Saydam, et al in the key finding that lung re-expansion is improved but no change in pleurodesis success following administration of intrapleural fibrinolytics is observed in patients with septated MPE(8, 9). This improvement could be due to an increase in fluid output of approximately 100ml in the urokinase group, although this difference did not reach statistical significance. Although different fibrinolytics were used in these studies, there is no reason to hypothesize any difference in efficacy between fibrinolytics. Intrapleural urokinase was not associated with any adverse reactions, suggesting it is safe for use in patients with MPE.

In light of these results, is it appropriate to insert a chest tube and attempt pleurodesis in patients with a septated MPE which is unlikely to drain? Given the high mortality demonstrated in this study, we propose that outpatient treatments (such as therapeutic aspiration or indwelling pleural catheter insertion) in conjunction with other palliative treatments for dyspnea (such as low dose opiates) may be more appropriate for this patient group, aiming at providing dyspnea relief without a hospital admission. Alternatively, thoracoscopy may allow more effective drainage prior to pleurodesis in those able to tolerate this procedure.

This study has several limitations. The study did not reach the original recruitment target. However, this occurred in light of new data on the minimal important difference in VAS used for measurement of dyspnea. On the basis of the data published during recruitment for this study, TIME3 would be adequately powered to exclude a clinically meaningful change in dyspnea following intrapleural urokinase. Completion of screening logs was variable between centres despite guidelines, with some sites including all patients with a chest tube for MPE whereas other sites only included patients fulfilling the eligibility criteria.

The TIME3 study results suggest important potential future areas of research. Indwelling pleural catheters (IPC) are increasingly used in the treatment of patients with MPE on the basis of randomised trials demonstrating improvement in dyspnea and reduced hospital stay(18). Recognised IPC complications include blockage and development of septations, which are increasingly treated with intrapleural fibrinolytics. A retrospective case series suggested improvement in pleural fluid drainage and radiographic appearance using intrapleural fibrinolysis(19), but this

study demonstrates these are not reliable surrogates for the key clinical outcomes of dyspnea relief and pleurodesis success. This suggests that prospective controlled trials are now required to assess the potential clinical benefit and harms of such treatment in IPC patients.

In summary, intrapleural urokinase does not improve dyspnea or pleurodesis success compared with placebo in patients with non-draining MPE treated with a chest tube and should not be routinely used as an adjunct to pleurodesis. This subgroup of patients have a high mortality and significant residual dyspnea despite chest tube insertion, and alternative palliative measures should be considered for the relief of dyspnea. The potential benefits of this treatment in improving hospital stay, chest radiograph appearances and mortality should be further investigated.

426 **Table 1**: Baseline characteristics of the 71 trial patients by group.

	Placebo (N=35)	**Urokinase (N=36)**
Age (yrs) mean (sd)	71·5 (8·3)	69·5 (10·5)
Female (%)	17 (49)	13 (36)
WHO Performance Status 0-2 (%)	21 (60)	21 (58)
Histological tissue type (%)		
Lung	12 (34)	10 (28)
Mesothelioma	5 (14)	4 (11)
Breast	6 (17)	6 (17)
Gastrointestinal	1 (3)	3 (8)
Adenocarcinoma of unknown primary	2 (6)	1 (3)
Ovarian	1 (3)	2 (6)
Other	8 (23)	10 (28)
Previously pleurodesed (%)	5 (14)	5 (14)
Size 12 French chest drain (%)	33 (94)	30 (83)
% opacification of	42 (21)	35 (20)

hemithorax by effusion (SD)			427
Baseline VAS score (mm) (SD)	38 (25)	38 (28)	

Figure legends

Figure 1: CONSORT diagram to summarise recruitment.

Figure 2: Mean change from baseline in VAS dyspnea following intrapleural urokinase or placebo. Circles represent mean VAS dyspnea over 28 days for individual participants, black line represents overall mean of group. Positive change represents less breathlessness.

Figure 3: Kaplan-Meier curve of time to pleurodesis failure

Figure 4: Time to death by group

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