Investigating the role of nebulised mucolytic therapy during lower respiratory tract infections post lung transplantation

Clinical Protocol

Background

According to the International Society for Heart and Lung Transplantation (ISHLT), the incidence of lung transplants per annum worldwide is rising annually, with over 3000 transplants completed according to the latest registry[10]. The Alfred is a state-wide, internationally renowned lung transplant service, transplanting between 59 - 79 patients over the last two calendar years, with a waitlist of more than 40 potential recipients. This makes it one of only 7 centres worldwide completing this volume of transplants[10].

Patients who have undergone lung transplantation for end-stage lung disease are subject to life-long immunosuppression to prevent allograft rejection. These patients are at a heightened risk of acquiring opportunistic lower respiratory tract infections (LRTI)[13], often characterised by sputum retention and / or production, which can have a negative impact on both morbidity and mortality[11]. Patients post lung transplant often find it difficult to clear secretions due to an alteration in normal physiology. Transplanted lung tissue is denervated upon resection from the donor, which has been shown to lead to slower cilial beat frequencies[12], impaired muco-ciliary clearance (MCC) rates[12-14] and an impaired cough reflex[25]. Devascularisation to lung tissue post ischaemic surgical time in the acute period can lead to an alteration in mucosal properties and structural changes around anastomoses, which may further impair the ability to clear secretions[11].

Inhaled, nebulised mucolytic agents are commonly used in the management of other suppurative chronic lung diseases characterised by excessive production of secretions. Dornase alfa acts by digesting the extracellular DNA released by inflammatory cells during infection[8]. It has been shown to have positive long-term effects on lung function in cystic fibrosis (CF)[8] and short-term benefits treating atelectasis and mucous plugging in acute, non-CF adult and paediatric cases[3-5]. Yet shown to be safe in normal subjects[8], it has been shown to have a detrimental effect on pulmonary function in non-CF bronchiectasis[17].

Inhaled saline acts by restoring the airway surface liquid layer of the mucosa, favourably altering mucous properties, accelerating MCC and stimulating cough[1-2]. Positive evidence exists for hypertonic saline (6-7%) in CF[1-2] and both hypertonic and isotonic (0.9%) saline in non-CF bronchiectasis[6]. There is discussion of clinical use of saline as a mucolytic in the post transplant patient[9] with no evidence by way of randomised controlled trial to demonstrate effect. There is no current evidence on the use of inhaled mucolytics post transplant.

Currently, both dornase alfa and saline (isotonic / hypertonic) are used in the inpatient and outpatient setting at this institution as a reactive treatment strategy for LRTI characterised by excessive sputum production and / or retention. We believe this warrants a short-term, randomised trial to assess the efficacy of current practice, and to evaluate whether dornase alpha is more effective than 0.9% saline, a cheaper, more accessible alternative.

Aim

To evaluate the efficacy of inhaled dornase alfa compared to inhaled isotonic (0.9%) saline on:

- Quantitative and qualitative respiratory outcomes
- The need for antibiotics, length of stay and exacerbation / re-admission rates

Hypothesis
Dornase alfa is more effective than isotonic saline in the post lung transplant population during LRTI.

Study design
Phase 2, assessor blinded, prospective randomised controlled trial.

Study population
Inclusion:
- Post bilateral sequential lung transplant
- Capable of performing airway clearance techniques / nebulisers
- Pulmonary exacerbation as defined by Fuchs et al[8]
- Must be productive of sputum

*As part of the Fuchs criteria screening, existing plain film CXR or CT scans taken as part of standard care will be used based on availability and the fulfilment of other criteria points to assess patient suitability.

Exclusion:
- Paediatric transplant <18yrs
- Single lung transplant – native lung physiology may confound outcome measures
- Interstate – unable to complete follow up
- Unable to perform lung function testing
- Unable to complete subjective outcome measures- unable to read English fluently
- Critically unwell / ICU / ventilator dependent
- Within 2 months of transplant date
  *Cystic Fibrosis will be stratified

Intervention
On admission to the ward as an inpatient, patients who give informed consent will be randomly assigned to one of two groups defined below. The randomisation sequence will be concealed using opaque envelopes. Randomisation will be stratified according to pre-transplant diagnosis (cystic fibrosis or not) as people with cystic fibrosis are expected to be younger and have a different underlying systemic disease process.

Treatment group: Once daily, 2.5ml inhaled dornase alfa (evening if able) with inhalational breathing routine (IBR). IBR consists of 4 slow deep breaths followed by 6 relaxed breaths, repeated until nebuliser is complete, coughing when the patient feels the need to expectorate. The patient will be instructed to sit in an upright position with upper limb support as able.

Control group: Once daily, 5ml inhaled 0.9% normal saline with IBR as above (evening if able).

All participants will undertake treatment for one month according to their allocated group, with follow up to 3 months, (2 months off randomised intervention). Both groups will continue to do their regular prescribed physical exercise routine over the course of the study.

Timing of assessment
All outcome measures will be performed at study baseline, 1 month and 3 months follow-up. Daily outcome measures used as a monitoring diary are an exception. There are no cough-specific quality of life questionnaires validated for use in the post lung transplant population.

Primary outcome

Lung clearance index (LCI) is a measure of ventilation inhomogeneity as measured during multiple breath washout (MBW) of inert tracer gases. It has been shown that this test is a potentially more sensitive measure of peripheral airway obstruction than regular spirometry in short term (4 week) mucolytic interventional studies in paediatric CF[18,19]. This test would be performed within the respiratory physiology lung function laboratory on site at all assessment points, by an assessor who is blinded to group allocation for follow up data collection.

Conventionally used primary endpoints in this population, such as regular spirometry[11], may be unable to detect between group differences without large sample sizes and long treatment durations. Based on current evidence from non-lung transplant populations, LCI has been able to show short-term change, whereas regular spirometry has not shown change [18,19].

Secondary outcomes – to be completed at specified follow up times as above

1. Regular spirometry (FEV1, FVC, FEF)
2. Cough specific quality of life (QOL)
    - Leicester Cough Questionnaire (LCQ)[24]
    - St. George's Respiratory Questionnaire (SGRQ)[23]

The LCQ is a 19-question tool, the SGRQ a 2-part questionnaire, both are validated QOL questionnaires used in chronic lung disease other than lung transplant

3. Inpatient days
4. Oral, inhaled or IVAB days (for LRTI only)
5. Number of hospitalisations
6. Exacerbations over study period – as defined by:
    - Presentation to hospital and commencement of antibiotics (oral, inhaled or IV)
    - Worsening of symptom scores (BCSS >1[20]), sputum colour score (BronkoTest colour 3-5)

7. C-reactive protein (CRP). An inflammatory marker measured with routine blood tests on admission with LRTI. Taken during IP stay and routinely on OP follow-up. Exisiting / available data only will be used – no extra routine bloods will be taken on account of study inclusion.

Secondary outcomes – to be completed daily

8. Self-reported symptom severity, used as a daily patient diary
    - Breathlessness, Cough and Sputum Scale (BCSS)[20]

The BCSS is a 12 point self-reported symptom severity score, validated for daily use in COPD

- Sputum colour score[22] – BronkoTest Ltd, London UK

Sputum colour has been shown to correlate with physiological infection in other chronic lung disease groups.

- Sputum quantity (nil, low, moderate, high)

Self-reported symptom scores are to be completed at the same time each day, prior to going to bed. They will be collected at each assessment interval as above. Treatment compliance will be measured by return of used and un-used medication packaging at each assessment point.

Sample size and power calculation
A total of 30 participants (15 in each group) will enter this design study. The probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 1.000 unit in LCI.
This is a conservative estimate that is smaller than previous differences found in paediatric populations[18,19]. This is based on the assumption that the standard deviation of the response variable is 0.94 units[18,19].

As a phase 2 study, this project is powered to detect differences in physiological outcomes, rather than quality of life or hospitalization. However, should the treatment prove to have physiological benefits, the secondary outcomes of this study will provide critical information for powering a future phase 3 trial.

Feasibility: Approximately 12 patients with pulmonary exacerbations are admitted under the lung transplant service each month (minimum estimate). We estimate that 70% will meet the eligibility criteria for the study and 50% will consent to participate. We therefore anticipate that it will be possible to recruit the numbers needed for this study in 8 months.

Statistical analysis
An intention to treat analysis will be conducted, with inclusion of all randomised participants, regardless of study completion. Data for continuous outcomes including LCI will be analysed using a linear mixed models analysis, which makes use of all available data at each time point and is less affected by incomplete data than analysis of variance. The likelihood of exacerbation or hospitalisation during the follow-up period for the dornase alpha group will be expressed as a relative risk compared to the isotonic saline group.

Bias / Confounders
There is potential for performance bias in this study due to the lack of ability to blind participants to their allocated treatment regimen. We are unable to package medications in a way other than that currently produced. We aim to outline, as part of the PICF, that both inhaled medications have proven to be efficacious (and detrimental in certain circumstances) in disease processes other than post lung transplant LRTI. Detection bias will be controlled by the use of a blinded outcome assessor for all follow-up data collection points.

Potential confounders in this study include the diagnosis of bronchiolitis obliterans (BOS), or chronic lung rejection, during which LRTI occurs simultaneously. Patients with a diagnosis of BOS may in fact demonstrate differences in lung physiology and ease of sputum expectoration, which may have an effect on outcomes variables. We feel that excluding these patients may have a detrimental impact on the external validity of this study, therefore we will stratify patients according to a diagnosis of BOS on study inclusion.

Outcomes and significance
This will be the first randomised controlled trial to analyse inhaled dornase alfa and isotonic saline in the post lung transplant population.
The outcome of this trial will help to guide physiotherapy and pharmacological management of post lung transplant patients with LRTI in the future, both nationally and internationally.

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