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ORIGINAL ARTICLE

Dornase alfa during lower respiratory tract infection post-lung transplantation: a randomized controlled trial

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SUMMARY

Lung transplant (LTx) recipients are at risk of lower respiratory tract infection (LRTI), while altered physiology may lead to difficulty clearing sputum. Mucoactive agents alter sputum properties and facilitate mucociliary clearance; however, there are no randomized controlled trials (RCTs) studying this post-LTx. This RCT evaluated the safety and efficacy of nebulized dornase alfa during LRTI post-LTx. Inpatient adults with LRTI and abnormal sputum following bilateral sequential LTx were eligible. Participants received 5 ml of isotonic saline, or 2.5 ml of dornase alfa, nebulized once daily for 1 month followed by 2 months symptom diary. Primary outcome was lung clearance index (LCI2%). Secondary outcomes included spirometry, quality of life, readmission, length of stay, self-reported exacerbations, and adverse events at baseline, 1 and 3 months. Thirty-two participated, 16 in each group, baseline mean (SD) FEV_1% 58 (22), median (IQR) length of stay 7 (5) days, time since LTx 3.49 (6.80) years. There were no significant between-group differences in LCI2% at any point (1 month mean difference −0.34, 95% confidence interval (CI) −1.57 to 0.89; 3 months −0.76, 95% CI −2.29 to 0.78, favoring dornase alfa). Secondary outcomes were not different between groups. These results do not support the routine use of dornase alfa during LRTI in LTx recipients.

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Introduction

The incidence of lung transplantation (LTx) is rising, with >4000 completed per annum [1]. Patients post-LTx are subject to lifelong immunosuppression to manage allograft rejection [2], increasing the risk of lower respiratory tract infection (LRTI) [3,4]. Resulting secretion burden can negatively impact on hospitalization [1], morbidity, and mortality [4]. Lung transplant recipients have difficulty clearing secretions because of altered respiratory physiology such as denervation, which can slow cilial beat frequency [5], impair mucociliary clearance (MCC) [3,5,6], and diminish cough reflex [7,8]. Ischemia and devascularization alters mucosa, causing structural change around anastomoses, further impairing secretion clearance [4].

Nebulized, inhaled mucoactive agents are often used in suppurative lung disease. Dornase alfa, a mucolytic, digests extracellular deoxyribonucleic acid (DNA) released during infection [9–11]. Dornase alfa has

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positive long-term effects on lung function in cystic fibrosis (CF) [9,12], with promise in severe, acute asthma [13]. There have been reports of atelectasis and sputum plugging resolution in acute, non-CF adults, and pediatrics [14–17]; however, robust trials in pediatric bronchiolitis and tracheomalacia [18,19], as well as mechanically ventilated adults [20–24] report no benefit. Dornase alfa may also be detrimental, negatively affecting lung function and exacerbations in non-CF bronchiectasis [22,25,26]. Prospective safety and efficacy of dornase alfa following LTx has not been studied.

Other mucoactive agents include expectorants, such as isotonic saline (IS), which may restore the airway surface liquid layer, favorably altering sputum properties, accelerating MCC, and stimulating cough [27]. In non-CF bronchiectasis [28,29], short-term IS use (≤3 months) was inferior to hypertonic saline (HS), while in COPD, IS improves symptoms but has no impact on respiratory function [22,30,31]. In pediatric LTx, HS has been retrospectively studied, showing no benefit [32].

Escalation to dornase alfa following IS is an anecdotal reactive treatment for LRTI characterized by sputum burden [33–35], leading us to believe that dornase alfa would be superior to IS. However, there remains no definitive evidence for any nebulized, inhaled mucoactive agent post-LTx [22]. There was a need for a randomized controlled trial (RCT) to assess the safety and efficacy of dornase alfa compared to IS, a cheaper, more accessible alternative. This RCT aimed to evaluate the safety and efficacy of nebulized, inhaled dornase alfa compared to IS in LRTI >2 months post-LTx on (I) lung function and quality of life (QOL); (ii) antibiotic use; (iii) length of stay (LOS); and (iv) symptoms, exacerbations, and readmissions.

Patients and methods

Adult LTx recipients were recruited from a state-wide LTx center in Australia. Patients were eligible for inclusion if they were aged ≥18 years, post-bilateral sequential LTx, and capable of independent nebulizer therapy. Patients had to be admitted to hospital and productive of abnormal sputum, displaying at least 4 of 12 symptoms indicative of LRTI[9], treated with or without antibiotics (Appendix S1: Method 1). Exclusion criteria included single LTx, as native lung physiology may have confounded outcomes; inability to attend follow-up or perform multiple breath washout (MBW) at baseline; inability to read study materials; critically ill (i.e., critical care, intubated); or <2 months post-LTx, as natural recovery [36] and acute complications [37] may have confounded results. Written informed consent was provided, and this trial was approved by Alfred Health and La Trobe University human research and ethics committees.

This was an assessor-blinded, prospective RCT comparing IS with dornase alfa. Randomization was stratified according to a LTx indication of CF, as pre-existing upper respiratory tract colonization in CF recipients may affect LRTI management. Participants and therapists were not blinded because of differences in study medication. Dornase alfa requires refrigeration, whereas IS does not, and standard dosages vary from 2.5 ml (dornase alfa) to 5 ml (IS). Funding was not available to repackage and deidentify medications. Assessors were blinded to group allocation for all outcomes. Antibiotic choice and medical management was commenced prerandomization.

Following baseline assessment, participants were randomly assigned (1:1) into two groups using a computer-generated algorithm, with allocation sequence concealed by opaque envelopes. Intervention was inhaled via a Pari Boy® SX compressor with Pari LC Sprint® nebulizer (blue insert, mouthpiece), creating an aerosol of mass median diameter 3.5 μm, mass percentage <5 μm of 67%, and approximate nebulization time of 5 (dornase alfa) and 10 min (IS; Pari GmbH©, Starnberg, Germany).

Treatment: Once daily (nocte), 2.5 ml (2.5 mg) nebulized, inhaled dornase alfa with an inhalational breathing routine (IBR) designed for this study. This consisted of four moderate depth, slow controlled breaths followed by six relaxed breaths, coughing when needed for expectoration, repeated until nebulizer completion. Participants sat upright with upper limb support throughout. *Comparison*: Once daily, 5 ml nebulized, inhaled 0.9% IS with IBR as above. Based on existing literature, we felt that IS would serve as a control agent post-LTx with respect to lung function [22], and because of a lack of an existing safety profile in adult LTx recipients [22] and previous AEs in non-CF lung disease [25], once daily dosing was deemed appropriate for a novel RCT.

Participants undertook intervention for 1 month, with follow-up to 3 months, (2 months off-treatment). A 1-month treatment period was chosen as this was inline with current off-label approval practices for dornase alfa at our institution. Both groups continued to perform prescribed physical exercise, and were asked to withhold additional mucoactive agents and/or formal airway clearance techniques (ACTs) such as positive expiratory pressure (PEP) devices for the duration of the trial. Deviation from protocol occurred only on consultation with a senior physician in the event of: significant patient deterioration; risk of inpatient

readmission; or risk of transfer to critical care. Self-reported symptom severity was used as a daily exacerbation diary, completed at the same time each day, including the Breathlessness, Cough and Sputum Scale (BCSS) [38], sputum color score 1–5 (BronkoTest©, London, UK) [39], and subjective sputum quantity [nil, low (<10 ml), moderate (10–30 ml), high (>30 ml)].

Outcome measures were collected at baseline, 1, and 3 months. *Primary outcome*: Lung clearance index (LCI), which is a global measure of ventilation heterogeneity measured by MBW. Multiple breath washout was performed with the subject in a seated position, breathing a fixed tidal volume (1L) from functional residual capacity (FRC) via mouthpiece. Trained, blinded assessors measured LCI2% as per international guidelines (lung volume turnovers required to clear nitrogen to 2% of starting concentration), with an increase in LCI2% corresponding to deterioration [40]. Three maneuvers were performed with offline data analysis [41].

Secondary outcomes: (I) MBW: FRC, representing the volume of gas at end expiration, immediately preceding washout; gas mixing at the diffusion front, or acinar entrance (S_{acin}); and in the proximal, conductive zones (S_{cond}). An increase in either S_{acin} or S_{cond} represents an increase in ventilation heterogeneity (deterioration) [40,42]. (ii) Spirometry [43]: forced expiratory volume in 1-second (FEV_1); forced vital capacity (FVC); forced expiratory ratio. (iii) Health-related QOL: Leicester Cough Questionnaire (LCQ) [44]; St. George's Respiratory Questionnaire (SGRQ) [45–47]. (iv) Inpatient LOS. (v) Oral, inhaled, or intravenous antibiotic days. (vi) Rehospitalization. (vii) Exacerbations, defined by: presentation to hospital and commencement of antibiotics; worsening of symptom scores (BCSS >1 with ≥5 days of preceding stability [48]); or days reporting purulent sputum (BronkoTest© color 3–5) [48]. (viii) C-reactive protein (CRP) when collected for routine care. (ix) Self-reported symptom severity. (x) Adverse events (AEs).

We recorded bronchoscopy frequency and findings from medical records to provide an indication of increased procedural burden above routine surveillance, defined by bronchoscopy driven by a change in symptoms or potential infection rather than routine transbronchial biopsy. New diagnoses of chronic lung allograft dysfunction (CLAD) requiring admission were recorded. Treatment compliance was measured by return of used and unused medication packaging at 1 month.

A total of 30 participants were required for this superiority trial. The probability was 80% that the trial would detect a 1.00 unit difference between groups in LCI2%. This was a conservative estimate, smaller than previous differences found in pediatric populations [49,50], based on the assumption that the standard deviation (SD) of the response variable was 0.94 units [49,50] with two-sided significance set at $P < 0.05$.

Statistical analysis was completed using IBM® SPSS® Statistics Version 24. Intention-to-treat (ITT) analysis was conducted including all randomized participants regardless of intervention completion. Data are presented as mean [SD or standard error (SE)] or median [range or interquartile range (IQR)]. Data for LCI2% were analyzed using linear mixed models (LMM) with a fixed factor of group × time (baseline, 1, 3 month) interaction. General linear models were used to analyze other MBW outcomes, spirometry, and QOL. Baseline variables were included as an outcome rather than covariate unless otherwise stated. Time was included as a nominal (categorical) variable.

We analyzed CRP using a generalized LMM method by means of binary categorization (CRP <20; CRP ≥20) [51] with a fixed factor of group x time. Antibiotic days (≤14; >14) and purulent sputum days (≤10; >10) were analyzed using binary logistic regression derived odds ratios (OR). This was expressed as the likelihood of fewer antibiotic or purulent sputum days for the dornase alfa group. Multivariate analysis of variance (ANOVA) was used to control for baseline differences in FVC. Mann–Whitney *U* tests were performed for non-parametric data unless otherwise stated. Chi-square tests were used to compare categorical outcomes. Likelihood of readmission, AE, bronchoscopy, and deviation from protocol for the dornase alfa group were expressed as a relative risk (RR) compared to the IS group. Time to readmission was analyzed via Kaplan–Meier procedure.

Results

Between October 2013 and May 2017, 95 patients were assessed and 32 participants were recruited (Fig. 1). Twenty patients were excluded in accordance with respiratory isolation protocols. An additional two participants were recruited following the loss of MBW data in the IS group following equipment failure. These participants continued in the trial, and are included in the ITT analysis for all other outcomes. Despite completing baseline primary outcome analysis, one participant was unable to complete both follow-up MBW assessments, and another was unable to complete the 3-month MBW (both dornase alfa). Two patients were excluded owing to an inability to complete baseline MBW.

Baseline demographics are found in Table 1 and Appendix S1: Result 1. All participants were treated with

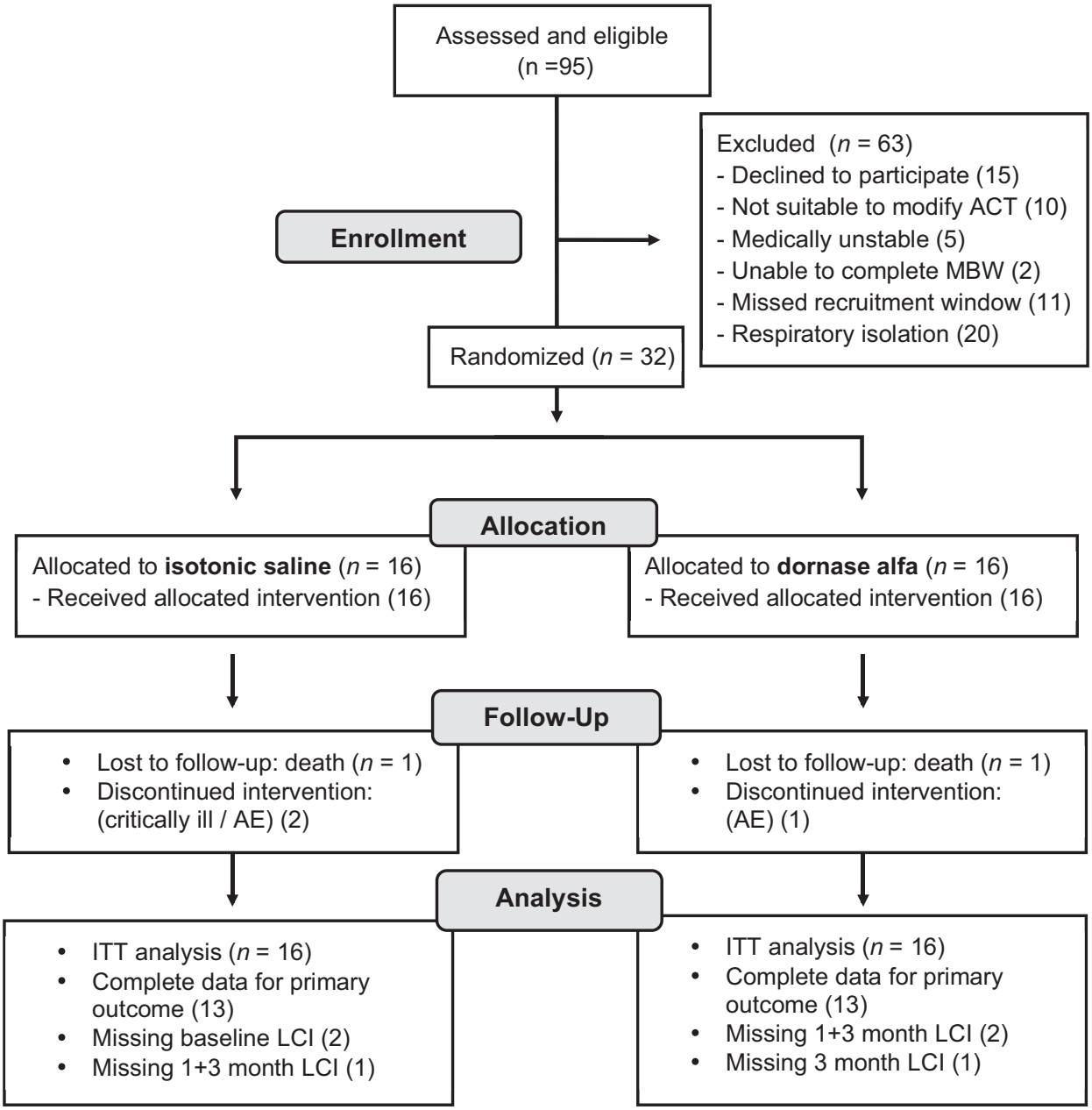

Figure 1 CONSORT diagram. ACT, airway clearance technique; AE, adverse event; CONSORT, consolidated standards of reporting trials; LCI, lung clearance index; MBW, multiple breath washout; *n*, number.

antibiotics at recruitment (Appendix S1: Result 2). The FEV_1 varied at baseline from 30% to 94% predicted, with FVC 38–88% predicted. The median (IQR) initial LOS was 7 (5.50–9.75) days for IS, and 6.5 (4.25–9.50) for dornase alfa. Medication adherence was assessed in 13 IS and 16 dornase alfa recipients over a mean (SD) treatment period of 31.81 (4.24) days. Median (IQR) adherence (days) was similar between groups, at 27 (23.50–31.00) days for IS and 28 (25.25–29.00) for dornase alfa ($P = 0.90$).

There were no significant between-group differences in the primary outcome (LCI2%) at any time point [1-month mean difference −0.34, 95% confidence interval (CI) −1.57 to 0.89; 3-months mean difference −0.76, 95% CI −2.29 to 0.78, $n = 26$, favoring dornase alfa] (Appendix S1: Result 3a), nor were there any differences in any other MBW or spirometry measure (Table 2). By removing the group x time interaction when analyzing LCI2%, the result ($P = 0.17$) was not altered. There was

Table 1. Baseline demographics.

Demographic	Isotonic saline (n = 16)	Dornase alfa (n = 16)
Age: mean (SD)	47.56 (15.99)	52.88 (10.77)
Days since transplant: median (IQR)	1497 (194.75–3014.50)	1162.5 (127.75–2559.25)
BMI (kg/m^2): mean (SD)	23.96 (6.10)	24.94 (4.95)
FEV1%: mean (SD)	53 (18.55)	62.5 (25.11)
FVC%: mean (SD)	59.81 (14.07)	75.81 (19.29)
FER: mean (SD)	69.31 (12.05)	61.56 (13.28)
Initial inpatient LOS: median (IQR)	7 (5.50–9.75)	6.5 (4.25–9.50)
CLAD: n (%)	5 (31%)	2 (13%)
Sinus disease: n (%)	2 (13%)	4 (25%)
GORD: n (%)	13 (81%)	12 (75%)
HLTx (n)	0	2
Gender (M/F)	7/9	11/5
MBW: mean (SD)	n = 14	n = 16
S_{acin}	0.354 (0.218)	0.337 (0.173)
S_{cond}	0.026 (0.023)	0.035 (0.026)
LCI 2%	11.05 (2.40)	10.31 (2.38)
FRC	1.83 (0.76)	2.32 (0.86)
Transplant indication: n (%)		
Cystic fibrosis	6 (38%)	5 (31%)
Bronchiectasis	0	2 (13%)
Interstitial lung disease	2 (12%)	0
COPD	6 (38%)	5 (31%)
Re-transplant	1 (6%)	0
A1AT	0	2 (13%)
Bronchiolitis obliterans	0	1 (6%)
PHTN / eisenmengers	1 (6%)	1 (6%)

A1AT, alpha-1 antitrypsin deficiency; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; FRC, functional residual capacity; GORD, gastroesophageal reflux disease; HLTx, heart–lung transplantation; LCI, lung clearance index; LOS, length of stay; MBW, multiple breath washout; PHTN, pulmonary hypertension.

no overall change in LCI2% within subjects across the trial period in either group (IS P = 0.33, dornase 0.60).

There were two deaths during follow-up, one in each group. Neither was deemed related to participation, with diagnoses of acute respiratory failure due to chest sepsis, and cryptococcal meningitis. The participant in respiratory failure deviated from protocol and was provided full respiratory therapy support. Both participants failed to complete MBW for all follow-up assessments due to critical illness.

Out of 16 participants, 3 reported AEs with IS, including shortness of breath (occasions = 2), chest tightness (2), chest pain (1), and headache (1). Out of 16 participants, 4 complained of AEs with dornase alfa, including shortness of breath (2), chest pain (2), hemoptysis (2), cough (1), and nausea (1). This led to treatment cessation in two participants, at 21 days due to shortness of breath and chest tightness (IS), and 7 days due to chest pain, cough, and nausea (dornase alfa). Risk of experiencing an AE was not significantly different between groups (RR 1.08, 95% CI 0.75–1.57).

During the intervention phase, four participants in the IS group required additional respiratory therapies for a median (range) of 10 (5–11) days, including additional mucoactive agents and PEP. This is compared to two participants in the dornase alfa group, requiring 24 (18–30) days of PEP and/or inhaled IS (RR 1.67, 95% CI 0.83–1.64). During follow-up, three participants in the IS group required PEP, additional mucoactive agents, and/or mechanical insufflation/exsufflation for 49 (29–57) days. Seven participants in the dornase alfa group commenced PEP, active cycle of breathing technique (ACBT), and/or nebulized mucoactive agents for 9 (2–68) days (RR 0.69, 95% CI 0.42–1.13). Deviation from protocol in days of additional respiratory therapy was not significantly different between groups (P = 0.13 intervention phase, P = 0.38 follow-up). Per-protocol analysis for LCI2%, excluding participants who deviated from protocol either in the intervention phase alone or at any point during the trial, can be found in Appendix S1: Results 3b and 3c respectively (P = NS).

Bronchoscopy was performed in 24/32 participants over the course of their LRTI (IS n = 11, 17 occasions, dornase alfa n = 13, 31 occasions, P = 0.15). Twice as many participants in the dornase alfa group underwent >1 bronchoscopy (n = 8) compared with IS (n = 4; RR 0.67, 95% CI 0.38–1.17). No other bronchoscopy marker was different between groups (Appendix S1: Result 4). There were no new CLAD diagnoses over the intervention phase, with three in the dornase alfa group and one in the IS group during follow-up.

There were no significant between-group differences in all-cause readmissions during intervention (RR 0.83, 95% CI 0.52–1.34) or follow-up (0.79, 0.54–1.15), or readmission LOS. Cumulative survival, expressed as percentage of participants remaining free from readmission at 30, 60, and 90 days was 81% vs. 63%, 63% vs. 38% and 50% vs. 18% in the IS and dornase alfa groups, respectively (Kaplan–Meier P = 0.07, Fig. 2). Time to first pulmonary-related readmission was not significantly different between groups (P = 0.58, Appendix S1: Result 5). The number of self-reported exacerbations

Table 2. Lung function.

	Baseline	1 month	3 months	*P*
MBW: mean (SD)				
S_{acin}				
IS	0.354 (0.218) *n* = 14	0.383 (0.227) *n* = 15	0.356 (0.188) *n* = 15	
Dornase alfa	0.337 (0.173) *n* = 16	0.348 (0.155) *n* = 14	0.354 (0.249) *n* = 13	0.89
S_{cond}				
IS	0.026 (0.023) *n* = 14	0.026 (0.037) *n* = 15	0.021 (0.027) *n* = 15	
Dornase alfa	0.035 (0.026) *n* = 16	0.045 (0.037) *n* = 14	0.033 (0.017) *n* = 13	0.84
LCI 2%*				
IS	11.05 (2.40) *n* = 14	11.65 (2.33) *n* = 15	11.19 (2.73) *n* = 15	
Dornase alfa	10.31 (2.38) *n* = 16	10.68 (1.97) *n* = 14	10.09 (2.19) *n* = 13	0.95
FRC				
IS	1.83 (0.76) *n* = 14	1.80 (0.72) *n* = 15	1.78 (0.76) *n* = 15	
Dornase alfa	2.32 (0.86) *n* = 16	2.03 (0.96) *n* = 14	2.22 (1.01) *n* = 13	0.31
Spirometry: mean (SD)				
FEV_1 l				
IS	1.65 (0.74) *n* = 16	1.76 (0.81) *n* = 15	1.78 (0.82) *n* = 15	
Dornase alfa	1.95 (0.77) *n* = 16	2.11 (0.68) *n* = 15	1.91 (0.88) *n* = 14	0.16
FEV_1%				
IS	53.00 (18.55) *n* = 16	58.33 (21.44) *n* = 15	57.60 (22.35) *n* = 15	
Dornase alfa	62.50 (25.11) *n* = 16	69.33 (25.35) *n* = 15	63.00 (27.94) *n* = 14	0.21
FVC l†				
IS	2.36 (0.85) *n* = 16	2.46 (0.91) *n* = 15	2.50 (0.89) *n* = 15	
Dornase alfa	3.10 (0.84) *n* = 16	3.21 (0.73) *n* = 15	2.96 (0.75) *n* = 14	0.58
FVC %†				
IS	59.81 (14.07) *n* = 16	62.07 (16.34) *n* = 15	63.73 (16.88) *n* = 15	
Dornase alfa	75.81 (19.29) *n* = 16	79.40 (18.07) *n* = 15	74.71 (17.02) *n* = 14	0.51
FER				
IS	69.31 (12.05) *n* = 16	70.87 (11.95) *n* = 15	70.27 (13.67) *n* = 15	
Dornase alfa	61.56 (13.28) *n* = 16	66.33 (14.03) *n* = 15	62.79 (17.13) *n* = 14	0.36

FER, forced expiratory ratio; FEV_1, forced expiratory volume in 1-second; FRC, functional residual capacity; FVC, forced vital capacity; IS, isotonic saline; l, liters; LCI, lung clearance index; MBW, multiple breath washout; mth, month; *n*, number.

P values represent overall change.

*Four participants recorded LCI 2.5%.

†Analysis of covariance controlled for baseline differences.

was low during intervention [mean (SD) IS 1.07 (1.00), dornase alfa 0.94 (1.00)], but increased during follow-up [IS 3.62 (2.02), dornase alfa 2.64 (2.02)]. This was not significantly different between groups, but did significantly increase within both groups between 1 and 3 months after cessation of intervention [IS 2.67 (2.19), $P = 0.001$, dornase alfa 1.71 (2.05), $P = 0.008$, Table 3].

We found no significant group x time interaction when analyzing CRP as a binary outcome ($P = 0.32$). The probability (OR) that dornase alfa use resulted in fewer (0–14) days of antibiotics was not significant during intervention (1.97, 95% CI 0.38–10.17) or follow-up (0.77, 0.19–3.17). Dornase alfa did not improve the probability of reporting fewer days with purulent sputum (0–10) during intervention (0.43, 0.10–1.89) or follow-up (0.59, 0.12–2.89; Table 3).

There were no significant between-group differences in SGRQ or LCQ (Table 4). Subjective sputum amount was generally 'low' (>65% across both groups and all time points, Appendix S1: Result 6). During intervention, there were positive microbiology findings in 75% and 81% of participants in the IS and dornase alfa groups, respectively. This reduced to 38% and 56% during follow-up. Antibiotic use fell to 63% (IS) and 56% (dornase alfa) during follow-up, however, there were no significant between-group differences (Appendix S1: Result 2).

Discussion

This is the first RCT to analyze the safety and efficacy of any nebulized, inhaled mucoactive agent during LRTI post-LTx. We found no significant differences between

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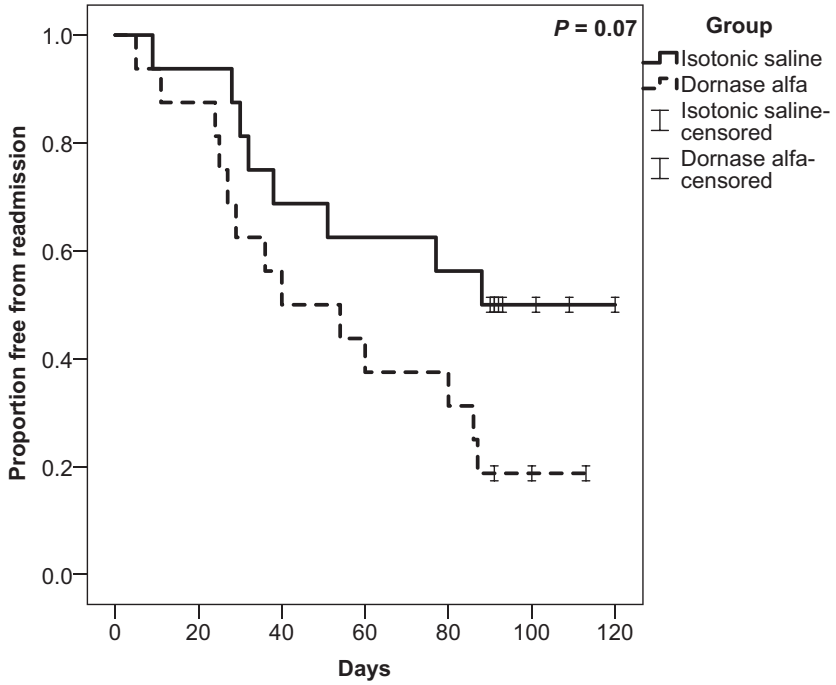

Figure 2 Kaplan–Meier all-cause readmission.

Table 3. Disease burden.

	Isotonic saline	Dornase alfa	RR (95% CI)/P
Antibiotic days: median (IQR)			
Intervention phase	25 (17.50–29.75)	23.5 (14.00–30.00)	0.42
Follow-up phase	10.5 (0–34.50)	14 (0–32.25)	0.72
Readmissions: all-cause (*n* = occasion)			
Intervention phase	4	8	0.83 (0.52–1.34)
Follow-up phase	8	12	0.79 (0.54–1.15)
Readmissions: all-cause days: mean (SD)			
Intervention phase	12.50 (15.76)	8.67 (3.88)	0.66
Follow-up phase	11.38 (10.07)	8.09 (7.73)	0.43
Readmissions: respiratory requiring AB (*n* = occasion)			
Intervention phase	2	7	0.60 (0.29–1.25)
Follow-up phase	6	6	0.92 (0.59–1.42)
Readmissions: respiratory days: mean (SD)			
Intervention phase	21.50 (20.51)	9.20 (4.09)	0.55
Follow-up phase	14.33 (9.99)	9.83 (9.24)	0.44
Exacerbations – BCSS number: mean (SD)			
Intervention phase	1.07 (1.00)	0.94 (1.00)	0.72
Follow-up phase	3.62 (2.02)	2.64 (2.02)	0.22
Purulent sputum days (color 3–5): median (IQR)			
Intervention phase	8.50 (4.00–18.25) *n* = 14	11.50 (5.50–22.50) *n* = 16	0.26
Follow-up phase	6.00 (1.50–15.00) *n* = 13	4.50 (0–22.50) *n* = 14	0.52
CRP: median (IQR)			
Baseline	29.50 (2.00–75.75) *n* = 12	6 (1.00–30.50) *n* = 13	
1 month	2.50 (1.00–32.00) *n* = 10	1.00 (1.00–9.25) *n* = 10	
3 months	1.00 (1.00–70.50) *n* = 10	12 (1.00–24.00) *n* = 7	0.32*

AB, antibiotic; BCSS, Breathlessness, Cough and Sputum Scale; CI, confidence interval; IQR, interquartile range; *n*, number; RR, risk ratio; SD, standard deviation; SE, standard error.

*Overall *P* value.

Table 4. Quality of life.

	Baseline	1 month	3 months	*P*
SGRQ: mean (SD)				
Symptom				
IS	53.35 (16.92)	61.93 (17.45)	51.47 (23.03) *n* = 14	
Dornase alfa	55.51 (19.59)	55.65 (19.25)	48.52 (17.54)	0.82
Activity				
IS	58.25 (21.34)	57.38 (22.59)	53.81 (29.58) *n* = 15	
Dornase alfa	50.37 (29.25)	40.82 (25.31)	53.18 (32.15)	0.17
Impact				
IS	34.06 (14.39)	30.72 (13.49)	33.90 (22.16) *n* = 15	
Dornase alfa	30.53 (17.61)	20.59 (17.47)	25.96 (21.54)	0.72
Total				
IS	44.69 (14.82) *n* = 16	43.58 (14.28) *n* = 13	40.81 (22.63) *n* = 14	
Dornase alfa	40.64 (19.78) *n* = 16	32.50 (17.98) *n* = 16	37.97 (22.75) *n* = 15	0.74
LCQ: mean (SD)				
Physical				
IS	4.69 (1.17)	5.12 (0.90)	5.69 (0.89)	
Dornase alfa	4.53 (1.04)	5.73 (0.86)	5.56 (1.25)	0.30
Psychological				
IS	4.95 (1.69)	5.87 (0.96)	6.05 (0.95)	
Dornase alfa	4.68 (1.35)	6.32 (0.87)	6.03 (1.35)	0.38
Social				
IS	4.95 (1.62)	5.75 (0.97)	6.07 (0.98)	
Dornase alfa	4.98 (1.57)	6.33 (0.77)	6.12 (1.18)	0.60
Total				
IS	14.60 (4.25) *n* = 16	16.72 (2.51) *n* = 13	17.81 (2.71) *n* = 15	
Dornase alfa	14.44 (3.88) *n* = 16	17.26 (4.62) *n* = 16	17.70 (3.69) *n* = 15	0.91

CRP: C-reactive protein; IQR: interquartile range; LCQ: Leicester Cough Questionnaire; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire.

P values represent overall change.

dornase alfa and IS for any outcome. Given that the average cost of the two interventions differs substantially ($AUD 1196 per patient, per month for dornase alfa vs. $AUD 3.33 for IS), the routine use of dornase alfa cannot be justified based on our data.

Both medications were well tolerated, with a low rate of AEs consistent with those previously reported [22]. Although withdrawal due to AEs was low, it is possible that these were due to intolerance of delivery method (mouthpiece) in patients with existing respiratory symptoms, rather than medication itself, due to 2/3 occurring in the IS group. Isotonic saline has been well tolerated in previously published RCTs in other respiratory diseases [22].

Self-reported exacerbations significantly increased in both groups during follow-up, suggesting that LTx recipients recovering from LRTI may be slow to improve and may require longer term intervention to prevent further morbidity [52,53]. There are independent associations between fungal and bacterial LRTI and the development of CLAD [54], which has a detrimental effect on patient-centered outcomes [55]. It is possible that a longer intervention period would have been more advantageous; this should be studied in future trials. Because of the lack of literature post-LTx, we cannot be certain that IS is a true control, despite this dose considered subtherapeutic based on use in other respiratory conditions [22]. Although beyond the scope of this trial, the addition of a no-treatment group would have enabled the assessment of IS efficacy as well as dornase alfa. We recommend this method in subsequent trials.

Although not statistically significant, the finding that more dornase alfa recipients required repeated bronchoscopy may be clinically important because of risk and cost [56]. Repeat bronchoscopy is used to monitor unresolved infective change [57] or to perform delayed transbronchial biopsy [58] secondary to secretion

burden. Despite this, we found no significant differences regarding risk of procedure or bronchoscopy findings. Time to first all-cause readmission may also be clinically important, as acute readmissions have an impact on resource allocation and healthcare cost. However, as readmissions unrelated to pulmonary etiology are common in the LTx recipient [59], we also chose to analyze pulmonary-related readmissions, revealing less between-group divergence by Kaplan–Meier analysis. As a result, we deemed freedom from readmission results to be of less clinical importance.

Based on current evidence from mucoactive trials in pediatric CF, LCI has shown short-term change in peripheral airway obstruction when regular spirometry has not [49,50]. In adult and pediatric LTx, LCI has been shown to be reproducible [60] and more sensitive to change in the presence of CLAD over spirometry, without the need for large samples and long intervention durations [61,62]. However, it can be unsuitable for patients with very severe lung disease, as MBW requires a tidal volume of approximately 1L (+FRC) [62]. Furthermore, patients with severe airflow obstruction have difficulty washing out nitrogen to achieve an LCI2% in a reasonable time frame [42].

This is pertinent to our cohort, highlighted by large variations in baseline FEV_1 and FVC, and the presence of clinically diagnosed CLAD at 31% (IS) and 13% (dornase alfa), increasing to 38% and 31% during follow-up. We note that no measure of MBW showed change, including S_{acin}, which is obtained after the first breath. All MBW values were abnormally high similar to previous studies [62,63]. It is therefore clear that despite small airway function in our cohort being similar to previous studies, gas mixing did not significantly change following administration of dornase alfa or IS.

Although not different at baseline, a potential confounder was pre-existing or new diagnoses of CLAD during which LRTI was a differential diagnosis. Patients with CLAD have impaired gas mixing through the airway tree [62,64] that can negatively affect sputum clearance. Although this could have affected results, excluding these patients would have negatively impacted on the external validity of these findings because of diagnostic differences in the detection of CLAD, the high prevalence of this syndrome internationally [1], and similarities in initial management between both CLAD and LRTI. Other limitations include the number of participants in both groups that deviated from protocol, commencing additional ACTs and/or mucoactive agents either independently or under senior clinician direction, which may have made it more difficult to detect a true difference in outcomes and/or diluted the effect of the intervention. Per-protocol analysis, although underpowered, suggests no effect.

There was potential for performance bias because of the lack of participant blinding. As a result of infection control policies, we were unable to include patients isolated with suspected or confirmed viral respiratory infection, although dornase alfa would not typically be indicated in acute inflammatory syndromes in the absence of abnormal secretions. There is scope to pursue further research in stable outpatients or inpatients with conclusive diagnoses of bacterial LRTI, during which dornase alfa may be more effective in the presence of purulent sputum [65,66]. Results should be interpreted acknowledging that this was a single center trial conducted in patients beyond the 2-month early postoperative recovery period.

Conclusion

This was the first RCT to examine the effects of a nebulized, inhaled mucoactive agent post-LTx. There was no increased risk of AE with dornase alfa use; however, there were no significant between-group differences in the primary endpoint of LCI2%, or indeed, any other secondary trial endpoint. These findings do not support the routine use of nebulized, inhaled dornase alfa during LRTI characterized by abnormal sputum production.

Authorship

BJT: takes full responsibility for the content of the manuscript, including the data and analysis. BJT: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. GS, SI, BB, BT and AH: contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Conflicts of interest

The authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supplementary Information.

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