ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Research letter

The role of High Flow Nasal Therapy in Bronchiectasis – A Post-hoc Analysis

W. R. Good, J. Garrett, H.-U. P. Hockey, L. Jayaram, C. Wong, H. Rea

Please cite this article as: Good WR, Garrett J, Hockey H-UP, *et al*. The role of High Flow Nasal Therapy in Bronchiectasis – A Post-hoc Analysis. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00711-2020).

The role of High Flow Nasal Therapy in Bronchiectasis – *A Post-hoc Analysis*

Good WR[1,2], Garrett J[2], Hockey H-UP[3], Jayaram L[4,5], Wong C[1,2], Rea H[1,2]

[1]Department of Medicine, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand.

[2]Department of Respiratory Medicine, Middlemore Hospital, Counties Manukau District Health Board, Otahuhu, Auckland, New Zealand

[3] Biometrics Matters Ltd, Hamilton, New Zealand

[4]Department of Respiratory Medicine, Western Health, Melbourne 3011, VIC, Australia

[5]Melbourne Medical School, The University of Melbourne, Melbourne 3021, VIC, Australia

Take home message: High flow nasal therapy significantly reduced exacerbation rates and improved quality of life in patients with stable bronchiectasis. High flow nasal therapy is therefore a potential treatment option for patients with bronchiectasis.

Correspondence: Dr William Good, Counties Manukau District Health Board, Respiratory Medicine, William.Good@middlemore.co.nz

Grant Support: The original study was funded by Fisher and Paykel Healthcare Ltd

To the Editor:

High flow nasal therapy (HFNT) is a gas delivery system that provides heated and humidified air or supplemental oxygen by nasal cannula. The role of HFNT in airways disease has primarily focused on chronic obstructive pulmonary disease (COPD). Studies in patients with COPD have demonstrated improvement in quality of life scores and reduced acute exacerbations with HFNT use.[1,2]

Humidification therapy offers a promising management approach for patients with bronchiectasis because HFNT improves mucociliary clearance.[3] Improving airway clearance is vital for breaking the 'vicious cycle' of recurrent infections and airway inflammation.[4] Only one previous study, *Rea et al* [5]*,* has evaluated HFNT in patients with stable bronchiectasis. This was an open-label, randomized, controlled trial in patients with either COPD or bronchiectasis. Overall, it found that HFNT significantly decreased exacerbation days, increased time to exacerbation, and reduced exacerbation frequency compared to usual care. Quality of life scores also improved significantly with humidification therapy. However, the study did not assess benefit in patients with COPD or bronchiectasis separately.

We therefore decided to undertake a *post-hoc analysis* to evaluate the effect of humification therapy on the patients with bronchiectasis in the *Rea et al.* study. [5]

The full study methodology is described in the original manuscript.[5] In brief, the 12-month study recruited patients with either COPD or bronchiectasis, randomizing study participants to HFNT versus usual care. Specific bronchiectasis diagnosis was confirmed by high-resolution computed tomography (HRCT). This was an open-label study with no sham treatment involved. The treatment arm provided humidified air, fully saturated at 37°C at a flow rate of 20-25 L/min, delivered via Optiflow nasal cannulae connected to a MR880 humidifier (*Fisher and Paykel Healthcare, New Zealand*). Patients were instructed to use the equipment for 2 or more hours per day in their home with flow rates, either 20 or 25 L/min, set as per patient tolerance. The New Zealand Health and Disability Ethics Committee approved the study and all participants provided written informed consent.

Statistical analyses comparing HFNT and Control was done in the generalised linear model framework for normal or Poisson data, or with the proportional hazards survival model for time to first exacerbation, allowing inclusion of demographic variables (gender, ethnic group, age), number of respiratory admissions in previous year, and relevant pre-treatment covariate where available. Results are based on model adjusted predicted means.

Forty-five (41.7%) of the 108 study participants recruited had a diagnosis of bronchiectasis. Within the bronchiectasis group, 26 of the 45 (58%) were assigned HFNT. The mean age of HFNT patients in the bronchiectasis group was 63 years (SD 11.4) and for control patients 65 years (SD 13.9). In the bronchiectasis group 58% of HFNT patients were female as were 63% of control patients. Regarding smoking; 46% and 63% were ex-smokers in the HFNT and control groups respectively. Overall withdrawal rates and explanation for withdrawal during the study are documented in the initial study.[5]

In the patients with bronchiectasis, the modelled exacerbation rate was 3.48 per patient per year in the control group and 2.39 in the HFNT group, corresponding to a 31.3% relative reduction with HFNT (rate ratio 0.69, 95% CI 0·49–0·97; *p=0.03*) (*Table 1A*).

At enrolment, baseline lung function for the bronchiectasis group demonstrated: HFNT FEV_1 1.51L (SD 0.57), FEV_1 (% of pred.) 56.5% (SD 20.2); control FEV_1 1.05L (SD 0.42), FEV_1 (% of pred.) 42.42% (SD 15.2). At 12 months, there were greater increases in FEV_1 and FVC in the HFNT group than in the control group, although the results were not statistically significant (*Table 1B*).

The St. George's Respiratory Questionnaire (SGRQ) *Total* score at baseline in the patients with bronchiectasis was 46.6 units and 50.2 units for HFNT and control groups respectively, indicating poor health status. At 12 months the *Total* and *Impacts* components of the SGRQ score improved significantly in favour of the HFNT group compared to the control group (*Table 1B*).

Changes in mean 6-minute walking distance did not differ significantly between the HFNT and control groups for the patients with bronchiectasis.

Table 1 – Bronchiectasis Group Trial Endpoints

(A) Exacerbation endpoints

	HFNT	Control	Rate ratio	95% CI[#] of ratio	p value
Rate *#/patient/year*	2.39	3.48	0.69	(0.49, 0.97)	0.034
Annual exacerbation days *(geometric mean)*	10.3	29.9	0.32	(0.14, 1.02)	0.056
Days to 1st exacerbation *(Predicted median)*	84	54	0.70*	(0.35, 1.40)	0.316

(B) Secondary endpoints

	Change from baseline		**Difference (95% CI)**	**p-value**
	HFNT	**Control**		
FEV_1 (L)	0.145	0.035	0.11 (-0.037, 0.257)	0.139
FVC (L)	0.115	-0.104	0.22 (-0.031, 0.468)	0.084
Score of St. George's respiratory questionnaire†				
Total	-12.3	-1.2	-11.0 (-20.7, -1.3)	0.028
Symptoms	-16.9	-9.8	-7.1 (-21.0, 6.8)	0.308
Activity	-6.3	3.3	-9.6 (-20.7, 1.5)	0.087
Impacts	-14.7	-1.6	-13.1 (-23.7, -2.4)	0.018
6-minute walk distance (m)	-16.2	-33.3	-17.1 (-62.3, 28.1)	0.445

* Hazard ratio; # Confidence interval

†Scores range from 0 to 100, with low scores indicating improvement; a change of four or more units is deemed clinically meaningful.

This post-hoc analysis provides information on the effect of HFNT in patients with stable bronchiectasis. High flow nasal therapy significantly reduced exacerbation rates and improved quality of life compared to usual care. It is therefore a potential treatment option for patients with bronchiectasis.

The mechanism of action of HFNT is multi-factorial. Heating to 37°C and the resulting humidification improve ciliary function and mucus hydration, ensuring optimal mucociliary clearance.[3,6] In addition, the high flow delivered by HFNT exerts positive airway pressure, which has the associated benefits of improved alveolar recruitment, increased tidal volume, reduced work of breathing and improved dead-space washout.[7-9]

Our post-hoc analysis demonstrated that even with a relatively short duration of HFNT (average 1.7 hours/day), patients with bronchiectasis had improved outcomes. More recent studies focusing on patients with COPD have used a longer duration of HFNT (~6 hours/day).[1,2] Given patients with bronchiectasis suffer from impaired mucociliary clearance and ciliary dyskinesia as a result of chronic infection and neutrophilic inflammation, [4,10,11] it is feasible that HFNT benefited our study patients with bronchiectasis primarily through improved airway clearance. Further research investigating whether a longer duration of HFNT results in

additional benefit in patients with bronchiectasis is warranted. Other treatment options include HFNT for defined periods during the day at the time when patients undertake chest clearance activities, or overnight use.

There is a paucity of literature investigating HFNT and patients with stable bronchiectasis. Only the study by *Rea et al.* has included patients with stable bronchiectasis.[5] Similarly, only one study has investigated HFNT in patients with acute exacerbations of airways disease.[12] This feasibility study enrolled patients with coexisting COPD and bronchiectasis and found that HFNT increased mucus clearance and reduced dyspnoea.

There are several limitations that need to be highlighted. Firstly, this is a post-hoc analysis and, despite the radiologically-confirmed bronchiectasis diagnosis and clear inclusion criteria, this was not the study's primary patient group. Consequently, the study did not characterise the patients with bronchiectasis using severity scores and more detailed airway inflammation markers were not analysed. The sub-study size is small and, even though the results are favourable, further larger, multi-centre studies need to be undertaken for confirmation.

Overall, high flow nasal therapy with humidification is a promising treatment for bronchiectasis and further larger studies are required. This is particularly important given the limited treatment options available for patients with bronchiectasis.

References

1. Storgaard LH, Hockey H-U, Laursen BS, Weinreich UM. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. *International Journal of Chronic Obstructive Pulmonary Disease.* 2018;13:1195.
2. Nagata K, Kikuchi T, Horie T, et al. Domiciliary high-flow nasal cannula oxygen therapy for patients with stable hypercapnic chronic obstructive pulmonary disease. A multicenter randomized crossover trial. *Annals of the American Thoracic Society.* 2018;15(4):432-439.
3. Hasani A, Chapman T, McCool D, Smith R, Dilworth J, Agnew J. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. *Chronic Respiratory Disease.* 2008;5(2):81-86.
4. Boaventura R, Shoemark A, Chalmers J. Pathophysiology. In: Chalmers J, Polverino E, Aliberti S, eds. *Bronchiectasis (ERS Monograph).* Sheffield: European Respiratory Society; 2018:8–28.
5. Rea H, McAuley S, Jayaram L, et al. The clinical utility of long-term humidification therapy in chronic airway disease. *Respiratory Medicine.* 2010;104(4):525-533.
6. Kilgour E, Rankin N, Ryan S, Pack R. Mucociliary function deteriorates in the clinical range of inspired air temperature and humidity. *Intensive Care Medicine.* 2004;30(7):1491-1494.
7. Spoletini G, Cortegiani A, Gregoretti C. Physiopathological rationale of using high-flow nasal therapy in the acute and chronic setting: a narrative review. *Trends in Anaesthesia and Critical Care.* 2019;26:22-29.
8. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respiratory Medicine.* 2009;103(10):1400-1405.
9. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults. *Chest.* 2015;148(1):253-261.
10. Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. *European Respiratory Journal.* 2008;31(2):396-406.
11. de Iongh RU, Rutland J. Ciliary defects in healthy subjects, bronchiectasis, and primary ciliary dyskinesia. *American Journal of Respiratory and Critical Care Medicine.* 1995;151(5):1559-1567.
12. Crimi C, Noto A, Cortegiani A, et al. High flow nasal therapy use in patients with acute exacerbation of COPD and bronchiectasis: a feasibility study. *COPD: Journal of Chronic Obstructive Pulmonary Disease.* 2020;17(2):184-190.