Multidimensional assessment and tailored interventions for COPD: Respiratory utopia or common sense?

Vanessa M McDonald[1,2,4,] Isabel Higgins[1], Lisa G Wood[4,5], Peter G Gibson [2,4,5]

[1]School of Nursing and Midwifery, The University of Newcastle

[2]School of Medicine and Public Health, The University of Newcastle

[3]School of Biomedical Science, The University of Newcastle

[4]Department of Respiratory and Sleep Medicine, Hunter Medical Research Institute

John Hunter Hospital, New Lambton NSW 2305 AUSTRALIA

[5]Woolcock institute of Medical Research, Glebe, Sydney NSW

Corresponding Author:

Peter Gibson

Hunter Medical Research Institute

Locked Bag #1000

New Lambton NSW 2305 AUSTRALIA

Ph +61 40420146

Fax +61 40420046

Email: Peter.Gibson@hnehealth.nsw.gov.au

Methods:

The inclusion criteria were: age ≥55 years and stable asthma and or COPD, with airflow obstruction defined by a pre-bronchodilator forced expiratory ratio (FER) <0.7 and Forced Expiratory Volume in 1 second (FEV_1) <80%predicted. Ability to attend study visits and satisfactory English language skills were needed. Exclusion criteria included: significant co-morbidities that the study may have impacted on, or an anticipated life expectancy of <3 months.

The study was conducted according to the International Conference on Harmonisation Good Clinical Practice Guidelines and was approved by the Hunter New England Ethics committee. The ACTRN registration number is 12611001278921.

Treatment allocation

Participants were allocated to either the MDAIM intervention or usual care control groups, using pre-determined criteria (the postcode of the participants' residential address) and allocation was concealed from the referring and treating doctor.

Study Design

All eligible participants underwent a previously developed and tested single visit multidimensional assessment to measure clinical, functional, biological and psychosocial outcomes (Table 1).[1, 2] This assessment focused on the components of airway disease, co-morbidity, COPD self-management skills and risk factors (Table 1).

The intervention group participants were rescheduled for the following week, reviewed by the case manager and dietician and the care planning exercise was conducted. Subsequent visits were scheduled according to the treatment plan (table 1). The control group had their physician and pulmonary rehabilitation (PR) visits scheduled by their usual care treating team.

Participants were followed up at 3, 6 and 12 months for repeat multidimensional assessment. If the control participants had not yet completed their pulmonary rehabilitation programme (PRP) at 3

months, the study follow-up visit was postponed for a maximum of 4 weeks to enable completion of this aspect of usual care.

Participant flow

Thirty-six participants were recruited to the study and were randomised to the intervention (n=17) or the control (n=19) group (Figure 1). All participants in the intervention group and 17 in the control group completed the 3 month follow-up. There were 4 participants in MDAIM who experienced 5 adverse events that were secondary to the intervention treatment. Over 12 months there was 1 death in the MDAIM group and 2 in the control group. The cause of death in the intervention participant was cardiovascular disease, in the control group one participant died of respiratory failure and the other of renal failure.

Intervention

MDAIM

The intervention consisted of individualised management based on the baseline multidimensional assessment. A personalised care plan was developed by the study physician and case manager. The clinicians and participants agreed on the tailored interventions for each of the identified problems[3]. An inflammometry algorithm (Table 1 manuscript) was used to inform treatment decisions for airway inflammation, systemic inflammation, and mucus hypersecretion. Other tailored interventions were standardised according to best available evidence (Table 1).[1] The case manager coordinated the plan. The interventions were delivered over 3 months during individualised visits. PRP participation occurred concurrently.

Control

The control group received medical assessment, pharmacotherapy and ongoing management by a respiratory physician and referral to a PRP.

Procedures

QOL was assessed using the Saint George Respiratory questionnaire (SGRQ).[4] Airflow obstruction was assessed by spirometry (KoKo K313100 PDS Instrumentation, Louisville, CO, USA) to measure pre and post-bronchodilator FEV_1, FVC and FER according to ATS/ERS standards.[5] Predicted FEV_1 and FVC were calculated using NHANES III.[6]

Airway inflammation was assessed using induced sputum.[7] Lower respiratory sputum portions were selected from saliva, processed using dithiothreitol and differential cell counts obtained.[8]

Peripheral blood was collected for assessment of systemic inflammation, using high sensitivity C Reactive Protein (hs-CRP) analysed using the Siemans Healthcare Diagnostics (Marburg, Germany) ELISA. The analytical measurement range for this kit was 2.90 – 190mg/L.

Mucus hypersecretion was assessed using six items from the 1978 ATS/DLD Respiratory Symptom Questionnaire.[9] Participants reported on the presence, frequency, volume and colour of sputum expectorated. All other assessments are described in the online supplement and Table 1.

Analysis

Health status, measured by the SGRQ, was the primary outcome.[4] Secondary outcomes included: the number of problems detected using the multidimensional assessment, exacerbations, sputum cell counts and CRP. An intention to treat analysis was performed. All data were analysed using Stata 10 (Stata Corporation, College Station, Texas USA). Parametric results are reported as mean (CI) and non-parametric results as median (IQR). Parametric data analysis was performed using Students' paired and non-paired t-tests as appropriate and the Chi square test for categorical data. Non-parametric analyses were performed using the two-sample Wilcoxon Rank Sum, the Kruskal-Wallis test for more than two groups, and Fisher's exact test for categorical data. Poisson regression was used to analyse differences in hospitalisations between groups and the incident rate ratio (IRR) reported. Results were reported as significant when $p<0.05$.

Results

Number of clinical management problems

The intervention led to a statistically significant decrease in the number of clinical problems. The mean (CI) number at baseline was 10.2 (9-11.4) per participant for MDAIM. This was reduced to 6.4 (5-7.7); p=0.0001 after the intervention, which was also significantly fewer than the control group,

who post treatment had 10.3 (9.1-11.6) problems per participant (p= 0.0001). The mean change (reduction) in number of problems for the MDAIM was -3.8 (-5.3- -2.3) compared to 0.5 (-2.1-1.1); p=0.003 for the control group.

Lung Function

No differences were found between the groups in any of the lung function parameters.

Exacerbations

Over 12 months there were 46% (IRR=0.54; p=0.28) less admissions in the MDAIM group compared to control, however this did not reach statistical significance. Over 12 months there were fewer dropouts in the MDAIM; n=3 (17.6%) compared to control; n=8 (42%).

Individualised interventions received by the MDAIM group

Inflammation based management

The 5 participants with eosinophilic airway inflammation were all prescribed ICS at baseline. They received oral corticosteroids and the baseline median (IQR) sputum eosinophil % of 15.5 (7-15.7) decreased to 0 (0-4) (p=0.02) post intervention (Figure 1b manuscript). Sputum neutrophilia was detected in 6 (35.2%) participants. Targeted antibiotic therapy significantly improved and normalised sputum neutrophilia from a mean (CI) baseline sputum neutrophil % of 81.8 (72.1-91.5) to 55.8 (33.7-78.0) post intervention; p=0.02 (Figure 1c manuscript). CRP was >3mg/L in 11 (64.7%) of the MDAIM participants who were treated with simvastatin for 3 months. There was a significant reduction in CRP from a median (IQR) baseline of 9 (5-11) to 4 (1-5.3) mg/L post treatment; (p=0.02). To aid in mucociliary clearance, 11 participants with mucus hypersecretion received a positive expiratory pressure device with education and follow-up. Of these, 6 were also treated with nebulised hypertonic saline (6%, 10mL bd). At follow-up, mucus hypersecretion was present in only 4 of the 11 participants (p=0.04).

Table 1: Multidimensional Assessment and Individualised Management

Clinical Problem	Assessment and guiding principle for identification	Individualised Management
Airway Components		
Exercise intolerance	6 minute walk (6MW) distance < 350 metres [10]	Pulmonary rehabilitation and home based training
Airflow obstruction	FEV_1/FVC ratio <70%, and FEV_1<80% pred	Long-acting bronchodilator therapy [Table 2]
Airway inflammation	Induced sputum: Neutrophils >61%; Eosinophils>3%; Mixed = Neutrophils >61% & Eosinophils>3% [11]	Included tailored pharmacotherapy according to inflammation based algorithm [Table 2]
Frequent chest infections	≥ 2 antibiotic courses in 12 months for lower respiratory tract infections	Written action plan with antibiotic choice tailored to baseline sputum pathogens
Pathogen Colonisation	Sputum culture positive for a recognised bacterial pathogen	Written action plan with antibiotic choice tailored to baseline sputum pathogens
Mucus hypersecretion	A volume ≥ 25mls of mucus produced daily for the last week in the absence of an infection	Tailored therapy according to inflammation based algorithm[Table 2]
Oxygen desaturation	SpO_2 < 90% either at rest or during 6MW test	Investigation and implementation of domiciliary oxygen therapy and nasal CPAP
Co-morbidity		
Assessment tools	Defined as all comorbid medical conditions, that were current and significant.	Guideline based management
Anaemia	Haemoglobin <120g/L Female or <140g/L Male	Guideline based management
Anxiety Depression	Hospital Anxiety and Depression Scale (HADS) Anxiety domain score ≥8 or Depression domain score ≥ 8[12]	Counselling, Cognitive Behavioural Therapy +/- paroxetine 20mg daily
Cardiac dysfunction	NT-proBNP >1000fmol/ml; chest radiograph	Guideline based management
Dysfunctional breathing	Nijmegen questionnaire Total score ≥23[13]	Breath retraining, including pursed lip breathing, active expiration, diaphragmatic breathing, adapting specific body positions, and coordinating paced breathing with activities. Techniques were reassessed and reinforced throughout the intervention period.
Systemic inflammation	Hs-CRP >3mg/L	Tailored pharmacotherapy according to inflammation based algorithm
Obstructive Sleep Apnoea	Epworth sleepiness scale Score >8 suggests need for further investigation[14]	Investigation and implementation of domiciliary oxygen therapy and nasal CPAP
Self-management Skills		
Exacerbation management	Patient does not possess a WAP or does not use the prescribed plan during exacerbations	Written action plan and self-management education Improvement of knowledge
Inhaler device polypharmacy	Prescription of ≥ 3 different inhaler devices[15]	Minimise devices, inhaler technique education

Inhaler device technique	Technique rated as inadequate[16]	Inhaler technique skills
Non Adherence	Reported use of <80% of prescribed treatment	Correction of adherence
Risk Factors		
Smoking	Admit to smoking and exhaled CO ≥10ppm or deny smoking and show exhaled carbon monoxide ≥10ppm	Counselling plus Nicotine Replacement therapy or Varenicline
Malnutrition Overweight Obesity	BMI <20kg/m^2 BMI between 27 & 30 kg/m^2 BMI >30kg/m^2	3 pronged intervention tailored to BMI. All received an individualised dietetic intervention, delivered by an accredited practicing dietitian. Advice: the components of a balanced diet, promoting anti-inflammatory foods high in Omega 3 fatty acids, antioxidants and calcium for bone health. **Underweight** –Healthy intervention plus nutritional supplements and counselling. Dietetic information regarding weight gain, including a high protein (1.2-1.5g Protein per Kg Ideal Body Weight), high energy (120% of Estimated Energy Requirements) eating plan and a nutritionally complete oral supplement (Two Cal HN, Abbott Nutrition and/or Sustagen Hospital Formula, Novartis Nutrition). **Overweight** – Healthy intervention plus dietetic intervention that focused on weight reduction/weight maintenance through a non very low calorie diet.
Sarcopenia	DXA: Appendicular skeletal muscle mass index < 5.45kg/m^2 (female) and 7.26 kg/m^2 (males)[17]	Muscle resistance training and high protein diet
Activity limitation	Defined as self-reported impairment due to an inability to achieve personal activity goals	Pulmonary rehabilitation and home based training

6 MW – 6 Minute walk
FEV_1-Forced Expiratory Volume in 1 second
FVC -Forced Vital Capacity
CPAP- Continuous Positive Airway Pressure
SpO_2- Pulse oximeter Oxygen Saturation
HADS – Hospital Anxiety and Depression Scale
BMI – Body Mass Index
DXA –Dual energy X-Ray Absorptiometry Hs CRP –High sensitivity C Reactive Protein

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