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Effect of *Laooq-e-Katan* (Linctus of Flax mucilage) as an oral bronchodilator formulation on MRC Dyspnea scale in patients with COPD

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ABSTRACT

Purpose: The method of classifying COPD as well to monitor any therapeutic intervention in COPD patients depends largely upon spirometric measurements but unfortunately disability is weakly related to the measurements of lung function. However, Medical Research Council (MRC) dyspnea scale is a simple and valid method of categorizing patients with COPD in terms of their disability that could be used to complement FEV1 in the classification of COPD severity. With this reason the present study was designed to re-evaluate the efficacy of *Laooq-e-Katan* (Linctus of Flax mucilage) a well known Unani pharmacopeial formulation in treating dyspnea which has been measured by a simple and standardized Medical Research Council (MRC) dyspnea scale.

Material and Methods: In this study, 60 patients were included as defined by GOLD criteria. The patients were distributed randomly by the simple randomization into test and control group. The level of dyspnea was assessed with Medical Research Council (MRC) dyspnea scale.

Results: There were 25 patients with Grade-II, Grade-III, Grade-IV Dyspnea in the test group at day zero (Day 0), out of which 16 (64.0%) patients had improved in dyspnea to Grade-I and three (12.0%) patients to Grade-0. Whereas in the control group there were 22 patients in Grade-II and Grade-III, out of which only 6 (27.27%) patients improved to Grade-I and no patient was improved to grade 0 Dyspnea. At the end of the treatment there was statistical significant difference seen in the improvement of dyspnea in the test group when compared with the control group ($p = 0.009$).

Conclusion: Dyspnea is an important symptom that may impact quality of life in patients with COPD. MRC-D scale was shown to be simple, fast and intelligible measurement along with categorizing patients with COPD in terms of their disability.

Keywords: Chronic obstructive pulmonary disease (COPD), Dyspnea, Usr-e-Tanaffus, Linctus of Flax mucilage, MRC-D scale.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow obstruction is usually progressive and associated with an abnormal inflammatory response of the lungs to the noxious particles and gases [2-5, 8, 9, 12]. The COPD patient's experiences a wide variation in their level of disability. It may vary from daily activities restriction as a result of reduced pulmonary function, or limitations in the exercise tolerance. Clinical pulmonary function testing (PFT) plays an essential or an integral role in the management of patients with, or at risk for, respiratory dysfunction. It is a valuable screening test for evaluating respiratory symptoms (cough, wheeze, dyspnea, and chest tightness), abnormal physical examination findings (wheeze, crackles, cyanosis, and hyperinflation), and abnormal laboratory tests (chest radiographs, arterial blood gases, oximetry) [12]. This test provides objective lung function assessments that the clinician can correlated with highly subjective symptoms such as dyspnea [13]. NICE and all international guidelines recommended the use of Spirometry to confirm the diagnosis and assess the level of Severity in COPD and hence it remains the standard method for grading COPD severity in international treatment guidelines [12, 16, 17]. The Global Initiative for chronic obstructive lung disease (GOLD) has recommended both Spirometry and disease specific quality of life is monitored regularly to guide any changes in treatment [8].

Dyspnea is one of the major symptoms of COPD and it impairs quality of life in such patients. Moreover, dyspnea is defined as a subjective sensation of shortness of breath or difficulty breathing that involves different neurophysiologic and psychological mechanisms [6, 7,11]. People with COPD typically seek medical care because of dyspnea and these patients described their dyspnea as a sense of increased effort to breathe, heaviness, air hunger, or gasping [2, 6, 15]. It develops gradually over many years and eventually compromises the activities and quality of life of patients [1]. Dyspnea is noted initially only on heavy exertion, but as the condition progress it occurs with mild activity. In severe disease, dyspnea occurs even at rest [6, 14].

The current description of chronic obstructive pulmonary disease which includes chronic bronchitis, emphysema has pathology of airways narrowing (Bronchoconstriction). A comparative study of classical and modern literature reveals that Bronchoconstriction either due to spasm, inflammation, fibrosis, exudation or congestion had been mentioned in classical literature under different terminologies and nomenclatures which is now covered by the broad term COPD and the term Usr-e-Tannafus seems quite appropriate for dyspnea due to Bronchoconstriction features which is central to it and therefore is being used for the patients with COPD. The literal meaning of Usr-e-Tanaffus is "difficulty in breathing" and is used as a synonymous for dyspnea. The description of the COPD in classical Unani literature is available under different nomenclature such as Zeeq-un-Nafas; Rabu; Buhar; Intesab-un-Nafas etc. While going through the classical Unani literature by Unani Scholars, it is crystal clear that the mechanism of Bronchoconstriction (Tangi-e-Tanaffus) and Usr-e-Tanaffus given by Unani physicians is not much different from the Modern view.

Dyspnea or Usr-e-Tanaffus is seldom a complaint until the FEV1 has fallen below about 60 percent of predicted, but sometimes, some individuals with COPD are relatively free of dyspnea despite impressively low levels of FEV1 [2, 10]. Several instruments are available to assess dyspnea: Medical Research Council (MRC) dyspnea scale has been in use for many years to assess the effect of breathlessness on daily activities. Other dyspnea scales include the Visual Analogue Scale, Oxygen Cost Diagram, Borg Dyspnea Scale, and baseline or transitional dyspnea index for use in clinical practice. The MRC scale measures activity limitation or disability due to dyspnea rather than the severity of dyspnea itself, and thus, measures the chronic effect of disease.

Thus in the present study, dyspnea severity was evaluated by MRC-D scale. The MRC dyspnea scale is a simple and valid method of categorizing patients with COPD in terms of their disability that could be used to complement FEV1 in the classification of COPD severity. The MRC dyspnea scale has been use for many years for grading the effect of breathlessness on daily activities [11]. This scale actually measures perceived respiratory disability, the WHO definition of disability being "any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being". The MRC dyspnea scale is simple to administer as it allows the patients to indicate the extent to which their breathlessness affects their mobility. Whilst there is a well established relationship between MRC dyspnea grade and walking test performance, there has been no formal assessment of the categories of breathlessness used in the MRC dyspnea scale and other measures of impairment, disability and handicap [19]. The Medical Research Council (MRC–D) dyspnea scale was also highly recommended for primary care. The MRC-D contains 5 statements that describe varying degrees of breathlessness. The MRC-D is validated to quantify disability associated with dyspnea and correlates with lung function measurements and walking distance [2, 18, 20, 21]. Unani medicine has immense potential in the management of respiratory diseases as proved by numerous clinical trials, hence the need was felt to re-

evaluate the potential of a well-known Unani formulation in the management of COPDs and its common symptom dyspnea or Usr-e-Tanaffus as a better, safe and efficacious substitute to the existing treatment options on scientific parameters. The long term management of patients with Chronic Obstructive Pulmonary Diseases needs a combination of drugs having Bronchodilatory, Expectoratory, Mucolytic, Anti-viral, Anti-infective and Immunostimulating activities. Unani formulation used in the present study possesses most of the above mentioned activities. Which further make a need to attempt to re-evaluate the efficacy of this formulation on COPD patients in a controlled manner on internationally-accepted criteria to provide a sound basis for the use of this drug in COPD patients.

MATERIALS AND METHODS

Subjects:

Patients with stable COPD, as defined by GOLD, were recruited from Majeedia Hospital / HAHC Hospital, after the approval of Institutional Ethics Committee Jamia Hamdard, New Delhi on dated 20.03.2012. The patients were distributed randomly into test and control group. The entry criteria for the study were as follows: 1) a Known post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEVV1/FVC) ratio of < 70% and FEV1 50% ≤ FEV1 < 80% predicted (Moderate cases of COPD) based on Gold Criteria defined by WHO; 2) Patients who are willing to participate; 3) Patients of either sex; 4) Patient aged more than 18 years. Whereas 1) Patients aged less than 18 years 2) Patients having acute exacerbation of breathlessness 3) Patients having severe or very severe COPD 4) patients taking β-blockers/ACE inhibitors 5) Patients suffering from Diabetes Mellitus, Hepatic Failure, Renal Failure, Congestive Heart Failure 6) Pregnant and lactating mothers were included under the exclusion criteria from the study.

After obtaining the written informed consent, patients were randomized into two groups (30 in each group). One group was given the test drug and another group was given control drug. Patients will be explained details regarding the nature of study, the drugs to be used, and the study procedure. All eligible patients finished the following examinations on the same day: Complete Haemogram; Blood sugar; Sputum Culture; LFT; KFT; Chest X Rays; ECG; Spirometry.

Assessment of Mizaj (Temperament): Assessment of temperament was done according to the Ajnas-e-Ashara (10 classical principles used for assessing the temperament in Unani system of medicine.

Patients were followed up for six times and at each visit physical examination and clinical assessments of both groups were done and were recorded on the case record form (CRF). Assessment of efficacy was done using the following parameters:

Clinical parameters: Modified medical research council questionnaire for assessing the severity of breathlessness(MRC) was done in mid visit (21st day) and also after the completion of therapy; Spirometry as per GOLD standard was repeated after six weeks of continuous treatment; Assessment of safety of the procedure was made on the following parameters: Hematological assessment: CBC; Biochemical assessment: LFT, KFT which were repeated in mid and after completion of therapy for assessment of drug safety.

The study was design as a randomized standard drug controlled trial. All the patients in the test group was given Lauq-e-Katan (Linium usitatissimum L.), a Unani pharmacopeia formulation 10 gms thrice a day for 6 weeks, followed up at every week. Similarly patients in control group were given standard theophylline 200mg thrice daily for 6 weeks, followed up at every week.

Assessment of dyspnea:

The level of dyspnea was evaluated and graded as per "MRC-D Scale". The MRC-D contains 5 statements that describe varying degrees of breathlessness. Based on the patient's responses, the observer was able to grade the degree of dyspnea-related impairment.

Statistical analysis:

The patients were distributed randomly by the simple randomization using the RAND function in the Microsoft office excel into test and control group. All the investigation reports and clinical assessment data were collected and recorded on each visit. Data were analyzed using SPSS-PC with application of chi-square test for the statistical analysis of MRC-D scale at day-0; 21st day and at the end of the study. The observational data and the results were compiled and recorded after statistical analysis and are been presented in the form of tables and graphs and discussed in the preceding text.

RESULTS AND DISCUSSION

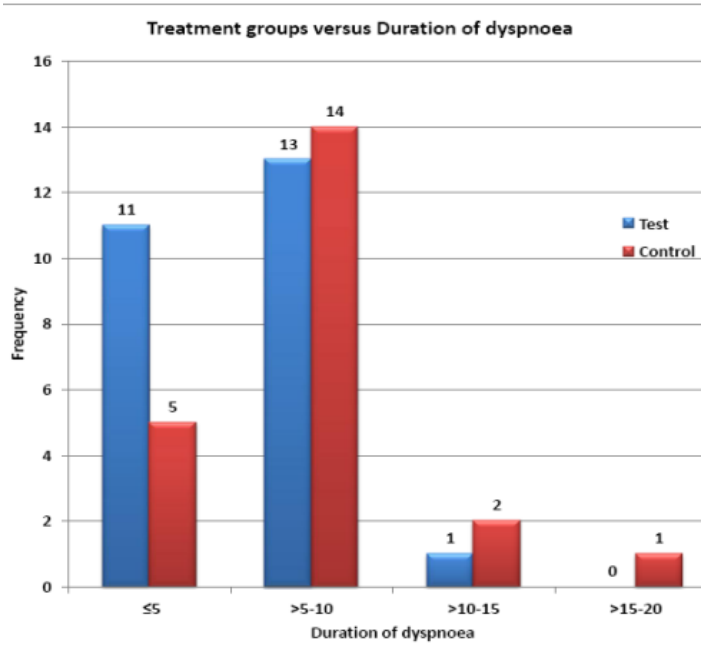
In the present study total number of completed patients was 47. There were 25 (53.19%) patients in test group and 22 (46.8%) patients in control group. The two groups were closely matched for the demographic observations including Age, Sex, Religion, Marital Status, Socio-Economic Status, Occupation, Dietary Habits, Family History, Past history, Seasonal Variation, Smoking Habits; Occupational exposure to dust and chemicals, Exposure of Smoke from Home Cooking, Temperament (Mizaj). Analysis of tables showed no statistically significant difference in the demographic pattern between the two groups at the start of treatment as quoted above, thus supporting randomization.

Patients with COPD described their dyspnea as a sense of increased effort to breathe, heaviness, air hunger, or

gasping. All the patients who were included in the study and followed till the end of the treatment in both the groups had dyspnea as a presenting complaint. In the test group 13 (52%) patients out of 25 had a history of dyspnea for more than 5 years, whereas 11 (44%) patients had a history of dyspnea less than 5 years. In the control group 14 (63.63%) patients had a history of dyspnea for more than 5 years, whereas 5 (22.72%) patients had a history of dyspnea less than 5 years. There was no statistically significant difference between the groups in dyspnea as presenting complaint at the time of inclusion or Day-0 (Table and Fig. No.1).

Distribution of Patients According to Duration of Dyspnea

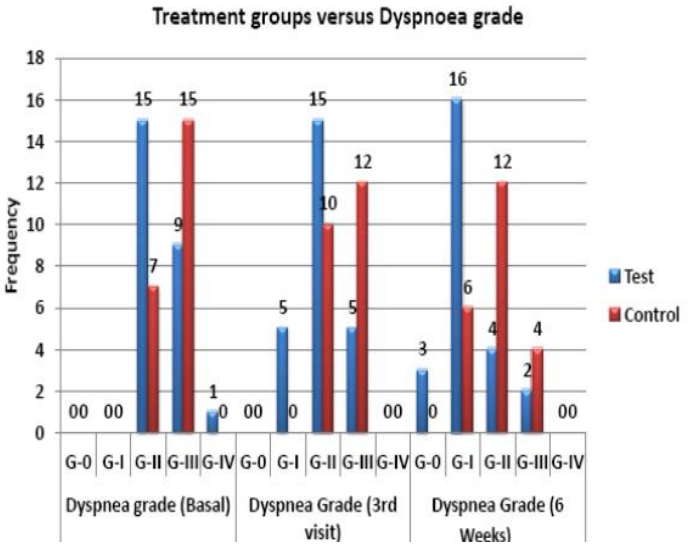
Duration of dyspnea (Years)	GROUP		Total	p value
	Test	Control		
≤5	11	5	16	p=0.444 (Chi-square test)
>5-10	13	14	27	
>10-15	1	2	3	
>15-20	0	1	1	
Total	25	22	47	



At day zero (day 0), the distribution of patients according to MRC-D Scale in the test group was 15 (60%) in Grade-II, 9 (36.0%) in Grade-III and 1 (4.0%) in Grade-IV whereas, in the control group patient was 7 (31.81%) in Grade-II, 15 (68.18%) in Grade-III and no patient in Grade-IV in the control group. There was no statistically significant difference observed between the groups with reference to dyspnea at day zero (day 0) (Table No.2 (a) and Fig No. 2).

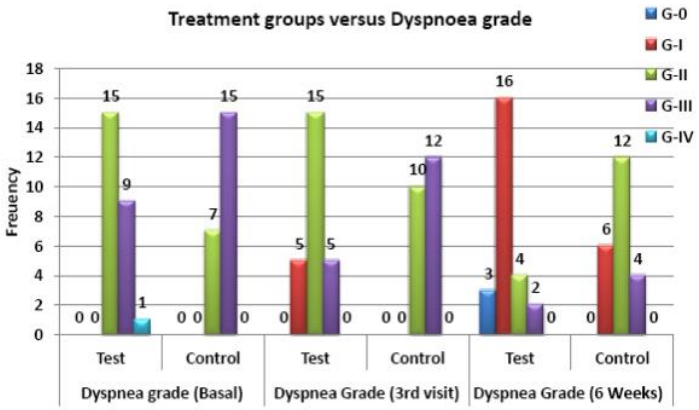
At 21st day (Mid visit) the improvement in dyspnea was statistically significant in the test (p = 0.013). The patients (5 out of 10) were improved from Grade-IV and Grade-III dyspnea to Grade-II and Grade-I dyspnea in the test group, so that there were 20 patients with grade I and II dyspnea. Whereas only 3 patients out of 15 patients improved in dyspnea from Grade-IV and Grade-III to Grade-II and Grade-I in the control group and there were only 10 patients were grade I and II dyspnea in the test group at mid visit. The Grade-I dyspnea was recorded in 5 (20.0%) patients in the test group, whereas no patients was improved to Grade-I in the control group after 21st day of treatment (Table No.2 (b) and Fig. No. 2).

Dyspnea grade (Basal)	GROUP		Total	p value
	Test	Control		
G-II	15	7	22	p=0.073 (Chi-square test)
G-III	9	15	24	
G-IV	1	0	1	
Total	25	22	47	



There were 25 patients with Grade-II, Grade-III, Grade-IV Dyspnea in the test group at day zero (Day 0), out of which 16 (64.0%) patients had improved in dyspnea to Grade-I and 3 (12.0%) patients to Grade-0. Whereas in the control group there were 22 patients in Grade-II and Grade-III, out of which only 6 (27.27%) patients improved to Grade-I and no patient was improved to grade 0 Dyspnea (Table No.2 (c) and Fig.No.2).

Dyspnea Grade (3rd visit)	GROUP		Total	p value
	Test	Control		
G-I	5	0	5	p=0.013 (Chi-square test)
G-II	15	10	25	
G-III	5	12	17	
Total	25	22	47	



At the end of the treatment there was again statistical significant difference seen in the improvement of dyspnea in the test group when compared with the control group (p = 0.009).

Hence the test group showed statistical significant difference in improving dyspnea. Dyspnea was relieved in most of the cases in the test group. This improvement in dyspnea may be attributed to the anti-inflammatory, bronchodilator and expectoral effect of the drug [22-29].

We should mention some of the limitation of the present study. Although, the present study was properly planned and executed according to the protocol and the best possible efforts were made to adapt the up-to-date methodology and clinical parameters as well as spirometric parameters as objective parameters to make it more scientifically valid. In spite of all these efforts certain limitations were observed during the course of like a small sample size and short duration of study. Since we recruited only stable patients from an OPD, the study sample may not to be representative of patients with exacerbation.

In the future, the study may be extended, with much larger sample size for more duration and prolonged follow up with modified pharmaceutical modification form of formulation. It may be designed as an overall adjuvant therapy to the standard international guidelines recommended for the management of Moderate as well as Severe cases of Chronic Obstructive Pulmonary Disease patients (COPD).

CONCLUSIONS

Since dyspnea greatly impacts the health related quality of life of patients with COPD and the MRC dyspnea scale is a simple and valid method of categorizing patients with COPD in terms of their disability. Therefore, it could be used to re-evaluate the efficacy of *Laooq-e-Katan* (Linctus of Flax mucilage) a well known Unani pharmacopeial formulation in treating dyspnea as well as to measure the disability along with spirometric parameters (FEV1, FVC, FEV1/FVC) in COPD patients who could be used to complement FEV1 in classification of COPD severity.

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