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Improvement in Quality of Life of Survivors of Chronic Obstructive Pulmonary Disease with Minimal Interventions

Prateek Upadhyay[1] and Prashant Ahlawat[2]*

[1]Department of Anaesthesia and Intensive care, Government Medical College and Hospital, Chandigarh, India
[2]Department of General Medicine, Government Medical College and Hospital, Chandigarh, India

Abstract

The global health care burden of Chronic Obstructive Pulmonary Disease (COPD) is enormous. Patients who are battling COPD have a very poor quality of life and suffer physically, mentally, emotionally, socially, and spiritually. Many treatment modalities have been in practice for a long time, but have limitations. The consequence of disregard for quality of life has generated a lot of unmet needs for patients. These patients deserve a good quality of life and a timely institution of palliative care to maintain the continuum of care. This article aims to highlight novel modalities, preferably non invasive or minimally invasive, that can be used to alleviate the suffering of patients with COPD. Lung flute is slowly finding its way into routine clinical practice for palliation of patients with COPD. It has the potential to be used as effortlessly as a hand-held incentive spirometer that is used in hospitals day in and day out. Bronchoscopic Lung Volume Reduction or Valve Surgery, Targeted Lung Denervation therapy, Metered Cryospray in addition to research on Stem Cell therapy are novel measures with hopeful and promising results so far to improve the quality of life of COPD survivors.

Keywords: COPD; Palliative Care; Quality of Life; Minimally Invasive Strategies; Emphysema; Elderly

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a commonly-encountered, preventable and treatable multifaceted inflammatory lung disease that has the characteristic features of limitation of airflow owing to airway and/or alveolar pathology, cough and dyspnea. It evidently and implacably impairs the quality of life of patients suffering from the disease [1]. Patients usually report to healthcare facilities when they develop an acute exacerbation of symptoms, and these exacerbations are financially and, mentally draining due to poor clinical outcomes, and associated with high morbidity as well as mortality. Therefore, managing an acute exacerbation must include decreasing the risks of further exacerbation as an imperative goal of treatment for any healthcare system, especially in high-prevalence areas [2, 3]. Currently, no definitive treatment is available to combat this condition. Therefore, it implies that all these patients require palliative care for the provision of a good quality of life and to maintain the vital functioning of the patients throughout the course of the disease, which is often lacking in quantity, as well as in the quality of care offered routinely.

Strategies to improve quality of life with minimal interventions

Contemporary medical therapy is predominantly centered on the addressal of the primary pathophysiology, i.e., inflammation and airway narrowing which is responsible for symptoms of airflow obstruction symptoms- shortness of breath, cough, chest tightness, and mucus production. It has its limitations and presents frequent and numerous unmet needs. Even with widespread application, the acceptance of and acquiescence to Metered Dose Inhalers (MDIs) are difficult to achieve. The general dispersion of drugs in the lung fields, particularly the periphery, remains a challenge for the treating physician. Moreover, in cases of super-added infections/inflammation, acute changes in lung physiology defeat the therapeutic effect of inhaled medications [4, 5].

Quality of life (QoL) is markedly reduced in COPD patients, necessitating the need for measures to improve QoL in a holistic approach to managing these cases. Prior longitudinal studies in a wide range of patients with COPD at the Global Initiative for Obstructive Lung Disease (GOLD) stage have constantly described an average decline rate in FEV_1 and FVC as ~30 mL/year and ~40 mL/year respectively on annual basis [6, 7]. Additionally, the decrease in FEV_1 specific for patients with stage II and III GOLD COPD is in the range of ~40–80 mL/year and~30–60 mL annually respectively [8,9]. Furthermore, Quality of Life measures have reported a decrease in COPD patients evident with an average increase in St George's Respiratory Questionnaire - COPD-Specific Version SGRQ-C of 1.2 to 1.8 points annually [6, 10]. The purpose of this review was to appraise the measures, preferably non-invasive or minimally invasive that could improve quality of life in COPD survivors who have often unmet needs and a brief update to familiarize the same for wider clinical application. There is ongoing research and innovations to improve the quality of life of patients with COPD are slowly evolving. Here, we describe the most clinically reasonable minimal invasive techniques.

Lung flute: Lung flute is a hand-held device approved by the FDA to supplement the mucus clearing ability of patients. Patients must blow vigorously through the mouthpiece of the flute, following which the breath passes through the *mylar reed*. This mechanism generates a sound wave in the range of 16 to 22 Hz with an output of 110 to 115 dB using 2.5 cm (s) of water pressure [11]. This sound wave then travels down the tracheobronchial tree and vibrates the tracheobronchial secretions. In return, this improves mucociliary clearance through the airways, resulting in induction of sputum.

***Corresponding author:** Prashant Ahlawat, Department of General Medicine, Government Medical College and Hospital, Chandigarh, India, Tel: +91-9115730617, E-mail: ahlawatprashant97@gmail.com

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With the use of this device, an improvement in health status demonstrated by the SGRQ score, a decrease in the incidence of acute exacerbations, and an increase in patient satisfaction was observed in a study by Sethi et al. enrolled 69 patients with COPD with chronic bronchitis for 26 weeks [10]. 85% of the patients enrolled in the lung flute group found the device effective and wanted to continue to use this device. Several other studies have also shown improvement in health status or stabilization of symptoms and reduction in acute exacerbations.

No adverse effects are observed related to the use of lung flute. However, the main drawback as in the above-mentioned study was the lack of objective measurement of increased mucociliary clearance.

A study by Elhawary A et al. later showed that sputum samples taken after induction using lung flute contained a higher number of cellular components, fibrinogen, elastase levels and a higher purulent score. thus, confirming that the mucus was derived from the lower respiratory tract [12]. Therefore, it is reasonable to conclude that this study established that the lung flute helps to remove mucus from the lower airways.

Bronchial rheoplasty: Bronchial rheoplasty is an endoscopic technique that uses nonthermal pulsed electrical fields to ablate the airway mucosa and mucus-producing cells of the airway epithelium. The procedure can be performed safely with monitored anesthesia care (MAC) and/or deep sedation under the supervision of a qualified anesthesiologist.

The system delivers a pulsed nonthermal electrical field that is of a high frequency but for a short duration, to the airway epithelium. This causes cell death by disrupting homeostasis, leading to cellular swelling and apoptosis. Meanwhile, the basic architecture of tissue is not distorted thus, allowing for epithelial regeneration later while reducing the goblet cells and hence decreasing mucus production. It is different from bronchial thermoplasty in terms of energy used.

Valipour et al. demonstrated that histological findings appear to confirm the proposed mechanism of action, displaying a statistically significant reduction in the number of epithelial goblet cells, particularly in those patients with pretreatment evidence of moderate to severe goblet cell hyperplasia [13]. These observations were accompanied by statistically significant reductions in CAT scores (COPD Assessment Test) and SGRQ scores (St. George's Respiratory Questionnaire) over a period of 12 months.

The main adverse event that could be related to this procedure is acute exacerbation, pneumonia, and mucosal scarring. In general, the procedure is safe and improves quality of life in patients with COPD and chronic bronchitis by decreasing mucus production, cough, and decreasing exacerbations.

Metered cryospray: Metered cryospray is a novel intervention that works similarly to bronchial rheoplasty by destroying the abnormal epithelium and mucous-producing goblet cells. This modality deposits liquid nitrogen with a radial spray head on the tracheobronchial airways with a high margin of safety to cause flash freezing at -196 deg. C. This mechanism then results in the formation of intracellular ice crystals. Therefore, the cellular structures are disrupted. However, the extracellular matrix is preserved, which facilitates epithelial growth [14].

In the basic design of the machine, there is the *REJUVENAIR system*. It basically is a console for the storage of liquid nitrogen, which is vented out by a catheter. It needs to be inserted through a flexible bronchoscope. The programmed doses are administered within a therapeutic safety margin using a specially developed algorithm in the bronchial airway. Cryoablation is targeted at the level of abnormal epithelium and superfluous mucous-producing goblet cells to a depth of 0.1–0.5 mm and a width of up to 10 mm [15]. After cryoablation, re-epithelialization of healthy mucosa has been demonstrated within 48 h [16].

In a study conducted by Garner et al., 34 patients received three treatments 4-6 weeks apart. After 3 months of initiation, investigators reported that there was a significant reduction in the COPD assessment test (durable for 6 months), the SGRQ and the Leicester Cough questionnaire (durable for 9 months). This study not only proved the safety of this modality, but also clinically significant improvements in the quality of life of patients with COPD were observed [17].

An ongoing randomized study named *SPRAY-CB* aims to compare metered cryospray with a sham procedure in patients with COPD and chronic bronchitis. (ClinicalTrials.gov Identifier: NCT03893370)

Targeted lung denervation (TLD): The pathophysiology of COPD is characterized by an exaggerated input of the autonomic nervous system into the lung and sensory signaling from the lung mediated by the vagus nerve. Excessive enhancement of parasympathetic tone in the lung causes an increase in cholinergic tone in the airways that, in turn, controls the tone of the smooth muscle layer of the airways, its reactivity and hyperresponsiveness, inflammation, and prolific mucus secretion [18-20]. This interferes with medical therapy, and hence, the treatment has several limitations and adverse effects.

Targeted Lung Denervation (TLD) therapy is delivered via a dual-cooled radiofrequency (rf) catheter designed to target and heat the tissue at depth. Hence, it results in a narrow band of ablation which offers the safety profile. The ablation is around the main bronchi and therefore its effect on the inner surface of the airway is minimal [21-23]. The net effect is targeted tissue ablation at depth with minimal heating and damage to the airway. AIRFLOW-1 was a randomized (1:1) double-blind multicenter study of 30 patients with moderate to severe symptomatic COPD who underwent TLD therapy [24]. After 3 years of observation, stability in lung function, sustained quality of life, and stability in exacerbations was found.

During 3 years of follow-up, no unexpected serious adverse events were observed.

Bronchoscopic lung volume reduction or valve surgery: Bronchoscopic Lung Volume Reduction (BLVR) or Valve Surgery is a simple procedure of about a 30-minute duration in which a one-way valve is placed in the emphysematous portion of the lung. This causes blockage of air entry into the lung and only trapped air may leak out, leading to resorption atelectasis of the diseased lung and inflation of the normal lung [25].

The rationale behind this procedure is as follows: [26]

- Improvement in the mechanical function of the diaphragm and intercostal muscles: This is achieved by decreasing the Functional Residual Capacity and returning the diaphragm towards its normal curvature and lengthened configuration.
- Improvement in left ventricular filling, end-diastolic dimension, and cardiac index due to decreased intrathoracic pressure.
- Reduction in lung volumes during exercise (that is, reduced dynamic hyperinflation), which is associated with reduced exertional dyspnea.

- Reduction in the inhomogeneity of regional ventilation and perfusion that improves ventilation-perfusion matching and results in improved alveolar gas exchange and effectiveness of ventilation.

In the *BeLieVeR-HIFi* trial, 50 patients were enrolled and divided into two groups of 25 each; the mean predicted FEV1% was 31.7%. The primary endpoint of the study was met as FEV_1 increased by 24.8% in the treatment group and by 3.9% in the control group [intergroup difference of 20.9% (95% CI 4.3% to 37.5%); $p = 0.033$]. This showed significant improvement in FEV_1 in the intervention group compared to the control group [27].

Similar results were seen in the IMPACT study, which was a prospective multicentre randomized control trial. Patients were divided into the EBV group plus standard of care (SoC) or SoC alone. 93 subjects were recruited and after a period of 3 months after the procedure, an improvement in FEV_1 from baseline was 13.7 ± 28.2% in the EBV group and -3.2 ± 13.0% in the SoC group (mean difference between groups, 17.0%; P = 0.0002) was observed. Other parameters also showed significant improvement in the EBV group, which were SGRQ and a walk distance of 6 minutes [28].

Thus, endobronchial valve placement avoids harmful effects of surgery and avoids the risks of anesthesia in elderly patients with COPD. Adverse effects associated with this strategy are minimal and rare, but pneumothorax is a dreaded complication, which should be managed promptly with preparations already made.

Stem cell therapy: Patients who are battling COPD have their lung tissues damaged due to an interplay of oxidative stress, cellular degeneration, and inflammatory insults. Stem cells are cells that have the ability to divide finitely or infinitely into either a cell, tissue, organ, or system. Similarly, depending on the differentiating potential, stem cells can be unipotent, multipotent, or pluripotent. Based on the origin of stem cells, they can be mesenchymal stem cells, hematopoietic stem cells, etc. In addition, depending on the source from which mesenchymal stem cells are derived, they can be derived from adipose tissue, bone marrow (BM), or umbilical cord (UC) mesenchymal stem cells (MSCs). Stem cells have provided medical researchers with an opportunity to improve the function and pliability of the system. They can help repair the tissue and have rejuvenation potential.

Stem cell therapy might exert its effects through the following mechanisms: [29]

- Reducing apoptosis of epithelial cells in the lungs.
- Improving the structure of damaged lung tissue.
- Promoting the proliferation of a variety of cells in the lung and facilitating the self-repair of lung tissue.
- Improving pulmonary function to some extent.
- Reducing systemic inflammatory response and promoting the secretion of a variety of anti-inflammatory mediators.

The first clinical trial of stem cell therapy in patients with COPD was carried out in Brazil from May 2009 to October 2009 [30, 31]. After 5 years of the first trial, Weiss et al. carried out a study using bone marrow (BM) MSC in moderate to severe COPD patients of category GOLD Stage II and Stage III. It was carried out in 62 patients who received 4 monthly infusions ($1*10^8$ cells/infusion) of stem cells and were followed for two years after the first infusion. It was noted in the study that there was a significant reduction in CRP levels after the first infusion with MSC in patients in whom baseline CRP was elevated; therefore, the possibility of the potential of stem cells to reduce systemic inflammation was theorized. This study did not reveal significant improvements in clinical symptoms or lung function tests, but sufficient evidence was provided regarding the safety of stem cell therapy [32].

The next question was when the stem cells were injected intravenously, whether they would circulate throughout the body or migrate directly to damaged lung tissue. Armitage et al. conducted a study to observe the distribution of stem cells after intravenous infusion along with the degree of systemic inflammation [33]. Nine patients received two infusions of allogenic BM-MSC, one per week for 2 weeks. The first infusion was labeled with Indium-111 dye to trace the location of cells. The dye-labeled MSCs were detected in the lungs within 30 minutes after injection and remained detectable after 24 hrs, after which they were distributed mainly in the liver. Furthermore, stem cells had a tendency to migrate towards healthy lung tissue compared to diseased or emphysematous lungs. This could be the reason for the absence of a significant improvement in lung function observed in the study. However, this study presented the inability of stem cells to stay in lung tissue for a long time, which could have hindered therapeutic benefits in stem cell treatment efforts.

Later, Oliveira et al. performed direct intratracheal administration of stem cells. In his study, ten patients of stage III or IV GOLD were randomly assigned to one of the two groups. One group received allogeneic BM-MSC and the other group received a 0.9% saline solution bronchoscopically, after which one-way Endobronchial Valve (EBV) was inserted. This facilitated the direct instillation of cells into the lung, and EBV helps in their retention. In the EBV with MSC group, no adverse effects were observed and a significant reduction in CRP levels was observed at 30 and 90 days compared to the EBV with the 0.9% normal saline group. The difference in pulmonary function tests was not significant between the two groups. However, patients who received MSCs had a significantly lower body mass index, dyspnea, exercise capacity index, airflow obstruction, lower modified Medical Research Council (mMRC) scores, and decreased Saint George's respiratory questionnaire (SGRQ) scores [34].

Thus, by increasing the dose of stem cells administered and by discovering a method to convince stem cells to stay in the damaged portion of the lung, COPD patients can receive a huge improvement in quality of life. Any improvement in lung function with stem cell therapy can influence and significantly improve the quality of life of patients with COPD [29]. Currently, several trials are ongoing to find an appropriate method, dose, and schedule of stem cell instillation for maximum benefit. However, a consensus is achieved to state that they are appropriate for use in patients with COPD, as their safety has been demonstrated in several trials in the past.

Conclusions

Survivors of COPD deserve compassionate, humane, and efficient palliative care to improve their quality of life and preserve vital functioning. Lung flute is slowly finding its way into routine clinical practice for palliation of Patients with COPD. It has the potential to be used as effortlessly as a hand-held incentive spirometer that is used in hospitals day-in and day-out. Bronchoscopic Lung Volume Reduction or Valve Surgery, Targeted Lung Denervation therapy, Metered Cryospray in addition to research on Stem Cell therapy are novel measures with hopeful and promising results so far in improving the quality of life of survivors of COPD.

A crucial factor in the productive implementation of these strategies is an optimal patient section, therapeutic approach, as well as an implementation in qualified centers. However, it is reasonable to be prepared for a potential complication, if any. In addition to the above-mentioned considerations, it is evident that these modalities are quite expensive and could burden the health care systems. The reduction in cost and development of lower-cost treatment modalities can only ensure a wider application and availability in resource-limited states and warrants research in this area.

Healthcare professionals should be familiar with the strategies and modalities described in this review, as they have the virtuous potential to be labeled as treatment of choice and standard of care in the near future. All that is left to be ensured is to observe the long-term effectiveness of these strategies, which is sure to be available soon with the ongoing clinical trials.

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