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Research Article

Longitudinal Assessment of FEV1 Change Following Autologous Cellular Therapy

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Abstract

Objective: Current pharmacologic management of Chronic Obstructive Pulmonary Disease (COPD) is aimed at improving symptoms and preventing exacerbations, yet none can alter the natural progression of lung function decline typical of the disease. Autologous-derived PRP-PC may prevent lung function decline and improve quality of life.

Methods: 281 patients with COPD underwent autologous cellular therapy with PRP-PC. Baseline lung function and quality of life data were collected and re-assessed after 3 months and after at least 12 months and compared to baseline.

Results: Participants undergoing autologous cellular therapy with PRP-PC had a and clinically significant increase in lung function after both 3 months and after at least one year with along with a significant improvement in subjective quality of life from baseline. Compared with findings in the literature that FEV1 typically declines over time, participants in this study had a significant increase in lung function on average.

Conclusion: Innovative treatments such as autologous cellular therapy can be a safe, effective option for preventing lung function decline over time. These therapies should be an option for patients where pharmacologic management has failed, or as an adjunct treatment.

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Keywords

Cellular Therapy; Autologous; Platelet Rich Plasma; PRP; COPD; FEV1

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a devastating, progressive, and life-limiting disease. It is currently the third leading cause of death in the United States and affects portions of all developing countries [1,2]. The annual projected mortality rate from COPD in the US is just over 4%, and the mean life expectancy is 13 years from the time of diagnosis with symptoms progressing and lung function declining during that span of time [3]. The most common symptoms are shortness of breath, activity intolerance, cough, anxiety and depression-however the experience of these symptoms is largely heterogeneous between patients [4]. Despite this heterogeneity, most people with COPD endorse their symptom burden as a significant problem in their daily life [5].

Over time, those with COPD lose lung function, symptoms become worse, and quality of life declines [6]. Sentinel work by Plato and Fletcher over four decades ago began to define the typical trajectory of lung function decline in patients with COPD. In 2012, researchers expanded on this work by publishing a large-scale analysis of several COPD studies to further define the phenomenon [7]. Attention to this decline and improving lung function over time should be a primary aim of COPD treatment. Though there are numerous pharmacologic treatments available, none have proven capable of altering the natural progression of lung function decline [8]. Innovative treatments, aimed at altering the advancement of disease, are needed urgently.

Current pharmacological treatments are intended to reduce symptoms, decrease frequency of exacerbations and increase patients' physical functioning, though there are no medications that are shown to alter long-term lung function decline [8]. Despite substantial strides in modern science, chronic lung diseases remain on the low end of the spectrum with regards to funding and attention to novel treatments [9].

This study examines the outcomes of 281 COPD-diagnosed participants who underwent autologous blood-derived Platelet Rich Plasma Concentrate (PRP-PC) treatment as an adjunct to their usual pharmacologic treatment. The primary aim of this study is to explore the changes in the Forced Expiratory Volume in 1 second of time (FEV1) 3 months and one year after treatment. The secondary aim of this study is to explore patients' subjective response to treatment at both time frames by measuring quality of life. The hypothesis is that cellular therapy, which can enhance a patient's own healing ability within damaged lung tissue, is a safe and effective option for maintaining and restoring lung function and positively affecting quality of life.

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Background

In almost all cases, COPD is caused by an injury to the lung tissue, particularly by cigarette smoking, though there is a small percentage of non-smokers who develop the disease along with those who inherit alpa-1 antitrypsin deficiency. Cigarette smoke activates a cascade of inflammation and injury that causes tissue destruction and persistent cellular dysfunction. Vascular Endothelial Growth Factor (VEGF), a naturally occurring reparative growth factor in the lungs is decreased significantly, even after the patient stops smoking [10]. Even in younger patients, COPD causes significant age-related features such as stem cell exhaustion, when healthy replacement cells for healing defective tissues can no longer be produced. Additionally there is a breakdown of normal protective mechanisms, and an increase in cell senescence with depletion of normal cells for replacement [10].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) categorizes COPD into four distinct stages of severity based on FEV1% predicted. A FEV1% predicted of >80% is mild, stage 1 disease; 50-80% predicted is moderate, stage 2 disease; 30-50% is severe, stage 3 disease and less than 30% is very severe, stage 4 disease. Therefore, as disease progresses, FEV1 declines. The sentinel study by Tantucci and Modina in 2012 analyzed several large-scale COPD studies to define expected FEV1 decline in terms of volume of air (in milliliters) over time. The authors concluded that the average yearly FEV1 volume decline for GOLD stage 2 is approximately 47-79 ml, stage 3 approximately 56-59 ml and stage 4-35 ml or less. Another large-scale study concluded that average FEV1 volume loss for all-stage individuals with COPD is approximately 17-46 ml per year [11]. While the US Food and Drug Administration and GOLD Committee endorse FEV1 volume change as the most significant indicator of change, others consider the percent change from baseline in FEV1% predicted to be the best indicator of lung function decline [12]. For this study FEV1% predicted percent change from baseline was the primary outcome assessed.

The diagnosis and surveillance of COPD and treatment is done largely by spirometry. Spirometry measures the amount of air that can be forcefully exhaled and measures the presence and degree of obstruction during exhalation. In COPD, the amount of air that can be forcefully exhaled in one second of time, the FEV1, determines the severity of obstruction. As obstruction increases, FEV1 decreases. FEV1 is measured against what would normally be expected in an equal patient without lung disease and is given as a percent of predicted.

Though spirometry is the most important quantitative measure of response to treatment, it is important to also consider the patient's subjective response. Given the heterogeneity of symptoms experienced, quality of life is best reported by the patient, and instruments have been designed specifically for understanding the burden of COPD symptoms. This study examines subjective quality of life measures as a secondary endpoint. The Clinical COPD Questionnaire (CCQ) has been widely used in multiple clinical settings and is endorsed by the Global Initiative for Chronic Lung Disease (GOLD) organization who sets the standards for the diagnosis of COPD. The CCQ is a 10-item scale composed of three domains (symptoms, mental status and functional status) with each item on a 0 to 6 scale, averaged into a 0-6 final score, with higher values indicating more severe symptoms [13]. Studies have tested the

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Minimum Clinically Important Difference (MCID) needed to detect treatment efficacy as a change of 0.4 or more from baseline [14,15].

Platelet Rich Plasma- Platelet Concentrate

Platelets- anucleate cells in the blood- have generally been thought of for their role in hemostasis. In recent years we have learned more about the role of platelets in inflammation and tissue repair [16]. We have learned that platelets are far more intricate- containing multiple proteins which are secreted from their alpha granules during activation and resulting in over 1500 bioactive factors which can participate in tissue repair and immune system modulation [17]. The most abundant growth factors secreted by activated platelets are Platelet-Derived Growth Factor (PDGF) which promotes collagen synthesis and stimulates proliferative activity, Transforming Growth Factor (TGF-β) which enhances collagen synthesis, promotes angiogenesis and promotes chemotaxis of immune cells, Vascular Endothelial Growth Factor (VEGF) which stimulates angiogenesis and the migration of endothelial cells, and Fibroblast Growth Factor (FGF) which promotes proliferation of mesenchymal stem cells [17]. Prepared PRP-PC is a pure source of signalling molecules that promote cell proliferation, migration, and differentiation and angiogenesis in their local environment [18].

Peripheral Blood Mononuclear Cells (PBMCs) are blood cells also found in PRP-PC preparations. PBMCs have round nuclei and play a major role in regulation of the immune response inclusive of lymphocytes (T and B-cells and natural killer cells) and monocytes. PBMCs can augment PRP-PC therapy by stimulating regeneration, including activation of VEGF and promotion of angiogenesis [19]. Preparation of PRP-PC for this study was created using the Harvest-Terumo SmartPrep® system from autologous whole blood. For the SmartPrep® equipment used for this study, 6 times baseline platelets are produced and 3 to 5 times baseline white blood cells are produced, according to independent studies [20]. For this treatment protocol prepared, autologous cells were administered same day to the participant on each treatment day over a period of two consecutive days.

It is presumed that activated platelets enter the lungs through the pulmonary first-pass effect and are trapped in the lungs' microcirculation close to areas of injury. Although the exact mechanism of action within the lung tissue remains under investigation, platelet-based therapy can enhance migration of therapeutic cells to areas of cellular injury, potentially shifting the balance from destruction to repair and healing [21]. Platelets can be quickly isolated and activated from peripheral whole blood using specialized centrifugation and returned to the patient's peripheral circulation the same day. Activated platelets release beneficial chemokines and growth factors that aid in coordinating the healing process [16]. Chemokines released from activated platelets also promote the recruitment, adherence, and proliferation of adult stem cells to further aid in tissue repair. More, biologically active growth factors, such as VEGF and PDGF recruit immune cells to support healing.

By mitigating the cyclical pattern of cellular destruction and faulty repair, we hypothesize that some participants treated with autologous, PRP-PC therapy will experience improvement in

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FEV1% predicted 3 months following treatment and that this improvement may persist for greater than 12 months following treatment. We hypothesize that post-treatment changes in FEV1% predicted will be statistically significant for COPD stages 2-4 and that participants will have a clinically significant improvement in participant-reported quality of life.

Subjects and Methods

281 participants included in this study underwent autologous, cellular therapy and were randomly selected from a pool of participants at two clinic sites. Preparation of PRP-PC for delivery to the lung tissue for this study was created using the Harvest-Terumo SmartPrep® system from autologous whole blood. After 60 ml of whole blood is collected from the peripheral circulation and combined with anticoagulant, the sample is transferred to a centrifugation vessel. Centrifugation concentrates the platelets and activates the release of bioactive growth factors along with a "buffy coat" layer of PBMCs. Red blood cells are sequestered and separated from the final product. The prepared product is then re-introduced to the patient's peripheral circulation through an intravenous catheter in the upper extremity.

150 participants were included in group A and were assessed at baseline and again at 3 months post-treatment. 131 participants were included in group B and were assessed at baseline and again after at least 12 months (mean 19.5 months) post-treatment. To evaluate if post-treatment FEV1% predicted changed significantly, baseline pulmonary function and quality of life data were collected prior to initial therapy and the same data were collected prior to the subsequent treatment. By selecting participants who returned for subsequent treatment, this allowed for pre- and post-treatment comparison and longitudinal analysis with the same pulmonary function equipment and processes.

Baseline and follow-up in-office spirometry assessed FEV1 absolute volume and FEV1% predicted using age, gender, ethnicity, height, and weight-adjusted measures. Data was inputted into the participants' electronic medical record for later data retrieval and analysis. Participant-reported quality of life was assessed at baseline and follow-up using the Clinical COPD Questionnaire (CCQ). The range of scores for the CCQ is 0-6, with higher scores representing lower quality of life. This score change is compared against the Minimum Clinically Important Difference (MCID) for an improvement in CCQ is 4 units (Alma, et. al.). CCQ data was also entered into each participant's electronic medical record for later data extraction. Both sites followed identical standard operating procedures in both the preparation and administration of cellular therapy, in the administration and documentation of spirometry data, and in the administration and documentation of quality of life measures.

All participants tolerated the procedure well, and there were no adverse or unexpected events reported. Because of the autologous harvest and preparation of PRP-PC it is immunologically safe and free from communicable disease such as HIV and hepatitis. Additionally, the risk of cell rejection after administration is eliminated with autologous cells. To mitigate the risk of cross-contamination, the commercial equipment used for PRP/PC separation is a closed-system, table-top and point-of-care centrifuge allowing only one specimen to be processed at

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a time. Finally, the site follows strict regulations set by the Food and Drug Administration (FDA) for the minimal manipulation of cells (without cryopreservation, expansion, or addition of growth factors) and same-day administration in all participants treated.

Informed consent was obtained on all participants prior to starting treatment. Permission for this study was granted by an independent Institutional Review Board. Prior to treatment, each participant underwent a history and physical examination. Pertinent medical records with diagnoses, medications, allergies, and surgeries were obtained from each participant prior to consideration for treatment and an approval process took place. To be considered for inclusion, participants had to have diagnosed COPD by an independent provider, be able to physically withstand travel to the treatment site and be free of a cancer diagnosis within the previous five years. Most participants travelled to the clinic from outside of the area. 90% travelled by car and 10% travelled by airplane. Participants were asked to be well-hydrated if not on a fluid restriction and all were encouraged to eat prior to treatment to minimize dizziness sometimes associated with the drawing of blood.

IBMs Statistical Package for the Social Sciences (SPSS) and IBM Amos were used in the data analysis. FEV1 data were analysed for statistical significance at $p < 0.05$. Paired-samples t-tests and Wilcoxon signed rank tests were used to compare pre- and post-treatment data. CCQ measures were compared against the 0.4-unit Minimum Clinically Important Difference (MCID) threshold for clinical significance.

Results

The mean age of participants in group A was 71.2 years (SD=7.6) and in group B was 73.1 years (SD=7.0). Approximately 60% of both groups were male and 40% female.

FEV1% predicted change for participants in both groups were descriptively analysed. For group A, the mean FEV1% predicted at baseline was 33.2% (SD= 18.3) and at 3 months was 34.7% (SD=19.2), a raw change of 2.47% (SD=30.2). The mean change in FEV1% predicted from participants' baseline was an improvement of 7.2% (SD=12.8). 12 months or more post-treatment, FEV1% predicted improved from 35.8% (SD= 17.1) at baseline to 38.1% (SD= 20.3). The mean change in FEV% predicted from participants' baseline was an improvement of 6.88% (SD=26.2).

For the 3-month follow-up group, a Wilcoxon Signed-Rank test was used because the normal distribution assumption of the data was violated. Shapiro-Wilk test was conducted to determine whether the differences in baseline and post-treatment at 3-months could have been produced by a normal distribution. The results of the Shapiro-Wilk test were significant based on an alpha value of 0.05, $W = 0.81$, $p < 0.001$. This result suggests the differences are unlikely to have been produced by a normal distribution, indicating the normality assumption was violated.

The results of the two-tailed Wilcoxon signed rank test were significant based on an alpha value of 0.05, $V = 3111.00$, $z = -3.37$, $p < 0.001$. This indicates that the differences between FEV1% predicted at baseline and FEV1% predicted at 3 months are not likely due to random

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variation. The median at baseline (Mdn = 27.00) was significantly lower than the median at 3 months post-treatment (Mdn = 29.00). Fig.1 presents a boxplot of the ranked values of baseline and follow-up.

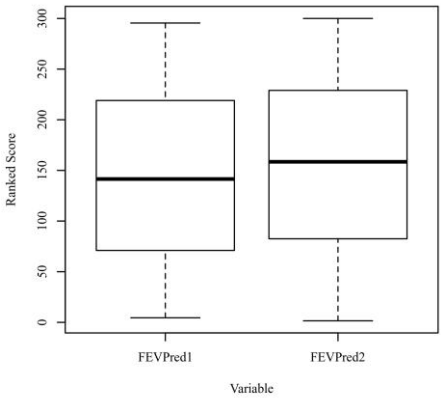

Figure 1: Ranked values of FEV1% predicted at baseline and FEV1% predicted at 3 months post-treatment.

A repeated measures analysis of variance (ANOVA) with one within-subjects factor was conducted to determine whether significant differences exist among FEV1% predicted at baseline and FEV1% predicted at 3 months post-treatment.

The results were examined based on an alpha of 0.05. The main effect for the within-subjects factor was significant, $F(1, 149) = 6.69$, $p = 0.011$, indicating there were statistically significant differences between the pre- and post-treatment FEV1% predicted values. Table 1 presents the ANOVA results. The means of the within-subjects factor are presented in Table 2.

Source	df	SS	MS	F	p	ηp2
Within-Subjects						
Within Factor	1	184.08	184.08	6.69	0.011	0.04
Residuals	149	4101.42	27.53			

Table 1: Repeated measures ANOVA results at 3 months post-treatment.

Variable	M	SD
FEVPred1	33.16	18.29
FEVPred2	34.73	19.22

Table 2: Means table for within-subject variables at 3 months post-treatment.

For the group evaluated at least 12 months post-treatment, a Wilcoxon Signed-Rank test was used because the normal distribution assumption was again violated. A Shapiro-Wilk test was conducted to determine whether the differences could have been produced by a normal

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distribution. The results of the Shapiro-Wilk test were significant based on an alpha value of 0.05, W = 0.91, p < .001. This result suggests the differences are unlikely to have been produced by a normal distribution, indicating the normality assumption was violated.

The results of the two-tailed Wilcoxon signed rank test were significant based on an alpha value of 0.05, V = 2624.50, z = -2.51, p = 0.012. This indicates that the differences between FEV1% predicted at baseline and FEV1% predicted after at least 12 months are not likely due to random variation. The median at baseline (Mdn = 32.00) was significantly lower than the median at follow-up (Mdn = 33.00). Fig. 2 presents a boxplot of the ranked values of baseline and follow-up.

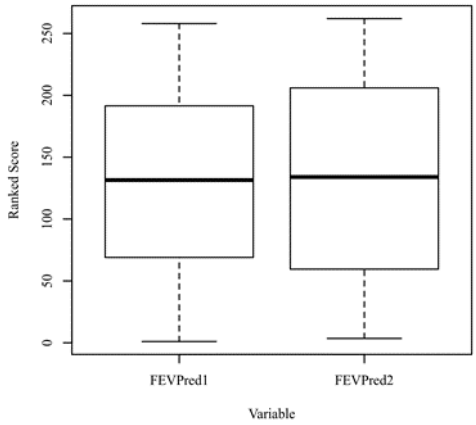

Figure 2: Ranked values of FEV1% predicted at baseline and FEV1% predicted at least 12 months post-treatment.

A Repeated Measures Analysis Of Variance (ANOVA) with one within-subjects factor was conducted to determine whether significant differences exist among FEV1% predicted at baseline and FEV1% predicted at least 12 months post-treatment.

The results were examined based on an alpha of 0.05. The main effect for the within-subjects factor was significant, F(1, 130) = 8.77, p = 0.004, indicating there were statistically significant differences between pre- and post-treatment FEV1% predicted values. Table 3 presents the ANOVA results. The means of the within-subjects factor are presented in Table 4.

Source	df		SS	MS	F	p	ηp2
Within-Subjects							
Within Factor	1		357.39	357.39	8.77	0.004	0.06
Residuals	130		5298.61	40.76			

Table 3: Repeated measures ANOVA results at 12+ months post-treatment.

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Variable	M	SD
FEVPred1	35.79	17.11
FEVPred2	38.13	20.3

Table 4: Means table for within-subject variables at 12+ months post-treatment.

Finally, the FEV1% predicted change from baseline was calculated as a percentage for each participant to determine those who improved by 15% or more from their baseline. At 3 months post-treatment, 23.3% of (n=35) participants improved by at least 15% from baseline. At 12 or more months post-treatment, 29% (n=38) of participants improved by 15% or more from baseline.

Quality of life measured by the CCQ showed a mean score at baseline of 3.6 and a mean score of 2.9 after 3 months. The mean change is an improvement of 0.73 (SD=0.83) from baseline and exceeds the minimum clinically important difference (MCID) of 0.4 for clinical significance. For those followed past one year, mean baseline CCQ score was 3.3 and follow-up mean score was 2.8. This shows an improvement of 0.56 (SD=0.9) from baseline and again exceeds the MCID of 0.4. At 3 months, 64% of participants (n=96) exceeded the MCID for improvement and at 12 months, 67.2% of participants (n=88) exceeded the MCID. Paired samples t-test on baseline CCQ scores and scores after 3 months and 12+ months were both statistically significant at $p < 0.000$ (CI -2.764, -0.370 and CI -3.897, -0.775 respectively).

Discussion

On average, participants undergoing autologous cellular therapy with PRP-PC experienced a statistically and clinically significant increase in lung function after both 3 months and after at least one year with along with a significant improvement in subjective quality of life from baseline. Compared with findings in the available literature that FEV1 typically declines over time, participants in this study had a significant increase in lung function on average. These findings suggest that PRP-PC may slow or prevent the typical, expected progression of COPD.

This study finds that cell-based therapy with PRP-PC for COPD is a safe, efficacious adjunct to traditional medical care and a valid alternative when traditional care fails. As the science continues to emerge and the exact mechanism of action of PRP-PC in the lungs continues to be explored, this study adds to the body of knowledge by showing both statistical and clinical improvements in quality of life and lung function over what would be expected after one year in a moderate-sized sample of participants. Furthermore, this study adds that administration of PRP-PC through infusion into the peripheral circulation was well-tolerated and without any adverse events.

The study was done using observation following intervention and was not designed as a clinical trial, and therefore limited by the lack of a control group. Further research should include a head-to-head comparison with standard of care and the use of matched controls. Due to the chronicity and often end-stage nature of the disease being studied here, we did not find it ethical

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to give placebo to a sub-group of participants therefore no participants in this study received comparative placebo.

Conclusions

Innovative treatments to prevent lung function decline in COPD are essential. Autologous cellular therapy with PRP- PC for COPD should be considered as an effective adjunct to ordinary pharmacological treatment or an alternative when other treatments fail. Cellular therapy is an innovative approach to the management of chronic lung disease which is needed urgently. Those participating in this study had both statistically and clinically significant improvements in FEV1 measures as well as clinically significant improvements in perceived quality of life following treatment. Contrary to the expected decline in lung function over time, this study finds an increase in lung function at two different time points following cellular therapy. Further, there is demonstrated safety by using autologous, minimally manipulated, and same day administered cells along with this strong profile of efficacy.

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